

COMPOSITIONS USEFUL AS INHIBITORS OF ROCK AND
OTHER PROTEIN KINASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application numbers 60/422,441, filed October 30, 2002, entitled "Compositions Useful as Inhibitors of Rock and Other Protein Kinases"; 60/476,433, filed June 6, 2003, entitled "Compositions Useful as Inhibitors of Rock and Other Protein Kinases"; 60/476,691, filed June 6, 2003, entitled "Compositions Useful as Inhibitors of Rock and Other Protein Kinases"; and 60/479,903, filed June 19, 2003, entitled "Compositions Useful as Inhibitors of Rock and Other Protein Kinases", and the entire contents of each of these applications is hereby incorporated by reference.

TECHNICAL FIELD OF INVENTION

[0002] The present invention relates to compounds useful as inhibitors of protein kinases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

[0004] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. (See, Hardie, G. and Hanks, S. *The Protein Kinase Facts Book, I and II*, Academic Press, San Diego, CA: 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the

substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (See, for example, Hanks, S.K., Hunter, T., *FASEB J.* **1995**, *9*, 576-596; Knighton *et al.*, *Science* **1991**, *253*, 407-414; Hiles *et al.*, *Cell* **1992**, *70*, 419-429; Kunz *et al.*, *Cell* **1993**, *73*, 585-596; Garcia-Bustos *et al.*, *EMBO J.* **1994**, *13*, 2352-2361).

[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease and hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0006] One kinase family of interest is Rho-associated coiled-coil forming protein serine/threonine kinase (ROCK), which is believed to be an effector of Ras-related small GTPase Rho. The ROCK family includes p160ROCK (ROCK-1) (Ishizaki *et al.*, *EMBO J.* **1996**, *15*, 1885-1893) and ROK α /Rho-kinase/ROCK-II (Leung *et al.*, *J. Biol. Chem.* **1995**, *270*, 29051-29054; Matsui *et al.*, *EMBO J.* **1996**, *15*, 2208-2216; Nakagawa *et al.*, *FEBS Lett.* **1996**, *392*, 189-193), protein kinase PKN (Amano *et al.*, *Science* **1996**, *271*, 648-650; Watanabe *et al.*, *Science* **1996**, *271*, 645-648), and citron and citron kinase (Madaule *et al.* *Nature*, **1998**, *394*, 491-494; Madaule *et al.*, *FEBS Lett.* **1995**, *377*, 243-248). The ROCK family of kinases have been shown to be involved in a variety of functions including Rho-induced formation of actin stress fibers and focal adhesions (Leung *et al.*, *Mol. Cell Biol.* **1996**, *16*, 5313-5327; Amano *et al.*, *Science*, **1997**, *275*, 1308-1311; Ishizaki *et al.*, *FEBS Lett.* **1997**, *404*, 118-124) and in downregulation of myosin phosphatase (Kimura *et al.*, *Science*, **1996**, *273*, 245-248), platelet activation (Klages *et al.*, *J. Cell. Biol.*, **1999**, *144*, 745-754), aortic smooth muscle contraction by various stimuli (Fu *et al.*, *FEBS Lett.*, **1998**, *440*, 183-187), thrombin-induced responses of aortic smooth muscle cells (Seasholtz *et al.*, *Cir. Res.*, **1999**, *84*, 1186-1193), hypertrophy of cardiomyocytes (Kuwahara *et al.*, *FEBS Lett.*, **1999**, *452*, 314-318), bronchial smooth muscle contraction (Yoshii *et al.*, *Am. J. Respir. Cell Mol. Biol.*, **1999**, *20*, 1190-1200), smooth muscle contraction and cytoskeletal reorganization of non-muscle cells (Fukata *et al.*, *Trends in Pharm. Sci* **2001**, *22*, 32-39), activation of volume-regulated anion channels (Nilius *et al.*, *J. Physiol.*, **1999**, *516*, 67-74), neurite retraction (Hirose *et al.*, *J. Cell. Biol.*, **1998**, *141*, 1625-1636),

neutrophil chemotaxis (Niggli, *FEBS Lett.*, **1999**, 445, 69-72), wound healing (Nobes and Hall, *J. Cell. Biol.*, **1999**, 144, 1235-1244), tumor invasion (Itoh *et al.*, *Nat. Med.*, **1999**, 5, 221-225) and cell transformation (Sahai *et al.*, *Curr. Biol.*, **1999**, 9, 136-145). More specifically, ROCK has been implicated in various diseases and disorders including hypertension (Satoh *et al.*, *J. Clin. Invest.* **1994**, 94, 1397-1403; Mukai *et al.*, *FASEB J.* **2001**, 15, 1062-1064; Uehata *et al.*, *Nature* **1997**, 389, 990-994; Masumoto *et al.*, *Hypertension*, **2001**, 38, 1307-1310), cerebral vasospasm (Sato *et al.*, *Circ. Res.* **2000**, 87, 195-200; Miyagi *et al.*, *J. Neurosurg.* **2000**, 93, 471-476; Tachibana *et al.*, *Acta Neurochir (Wien)* **1999**, 141, 13-19), coronary vasospasm (Shimokawa *et al.*, *Jpn. Cir. J.* **2000**, 64, 1-12; Kandabashi *et al.*, *Circulation* **2000**, 101, 1319-1323; Katsumata *et al.*, *Circulation* **1997**, 96, 4357-4363; Shimokawa *et al.*, *Cardiovasc. Res.* **2001**, 51, 169-177; Utsunomiya *et al.*, *J. Pharmacol.* **2001**, 134, 1724-1730; Masumoto *et al.*, *Circulation* **2002**, 105, 1545-1547), bronchial asthma (Chiba *et al.*, *Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol.* **1995**, 11, 351-357; Chiba *et al.*, *Br. J. Pharmacol.* **1999**, 127, 597-600; Chiba *et al.*, *Br. J. Pharmacol.* **2001**, 133, 886-890; Iizuka *et al.*, *Eur. J. Pharmacol.* **2000**, 406, 273-279), preterm labor (Niro *et al.*, *Biochem. Biophys. Res. Commun.* **1997**, 230, 356-359; Tahara *et al.*, *Endocrinology* **2002**, 143, 920-929; Kupittayanant *et al.*, *Pflugers Arch.* **2001**, 443, 112-114), erectile dysfunction (Chitaley *et al.*, *Nat. Med.* **2001**, 7, 119-122; Mills *et al.*, *J. Appl. Physiol.* **2001**, 91, 1269-1273), glaucoma (Honjo *et al.*, *Arch. Ophthalmol.* **2001**, 1171-1178; Rao *et al.*, *Invest. Ophthalmol. Vis. Sci.* **2001**, 42, 1029-1037), vascular smooth muscle cell proliferation (Shimokawa *et al.*, *Cardiovasc. Res.* **2001**, 51, 169-177; Morishige *et al.*, *Arterioscler. Thromb. Vasc. Biol.* **2001**, 21, 548-554; Eto *et al.*, *Am. J. Physiol. Heart Circ. Physiol.* **2000**, 278, H1744-H1750; Sawada *et al.*, *Circulation* **2000**, 101, 2030-2033; Shibata *et al.*, *Circulation* **2001**, 103, 284-289), myocardial hypertrophy (Hoshijima *et al.*, *J. Biol. Chem.* **1998**, 273, 7725-77230; Sah *et al.*, *J. Biol. Chem.* **1996**, 271, 31185-31190; Kuwahara *et al.*, *FEBS Lett.* **1999**, 452, 314-318; Yanazume *et al.*, *J. Biol. Chem.* **2002**, 277, 8618-8625), malignoma (Itoh *et al.*, *Nat. Med.* **1999**, 5, 221-225; Genda *et al.*, *Hepatology* **1999**, 30, 1027-1036; Somlyo *et al.*, *Biochem. Biophys. Res. Commun.* **2000**, 269, 652-659), ischemia/reperfusion-induced injury (Ikeda *et al.*, *J. of Surgical Res.* **2003**, 109, 155-160; Miznuma *et al.* *Transplantation* **2003**, 75, 579-586), endothelial dysfunction (Hernandez-Perera *et al.*, *Circ. Res.* **2000**, 87, 616-622; Laufs *et al.*, *J. Biol. Chem.* **1998**, 273, 24266-24271; Eto *et al.*, *Circ. Res.* **2001**, 89, 583-590), Crohn's Disease and colitis (Segain *et al.* *Gastroenterology*

2003, 124(5), 1180-1187), neurite outgrowth (Fournier *et al. J. Neurosci.* 2003, 23, 1416-1423), Raynaud's Disease (Shimokawa *et al. J. Cardiovasc. Pharmacol.* 2002, 39, 319-327), and atherosclerosis (Retzer *et al. FEBS Lett.* 2000, 466, 70-74; Ishibashi *et al. Biochim. Biophys. Acta* 2002, 1590, 123-130). Accordingly, the development of inhibitors of ROCK kinase would be useful as therapeutic agents for the treatment of disorders implicated in the ROCK kinase pathway.

[0007] ERK2 (extracellular signal regulated kinase) is a member of the mammalian mitogen-activated protein (MAP)1 kinase family. (MAP)1 kinases are serine/threonine kinases that mediate intracellular signal transduction pathways (Cobb and Goldsmith, *J Biol. Chem.*, 1995, 270, 14843; Davis, *Mol. Reprod. Dev.* 1995, 42, 459) and are activated by mitogens and growth factors (Bokemeyer *et al.. Kidney Int.* 1996, 49, 1187). Members of the MAP kinase family share sequence similarity and conserved structural domains, and, in addition to ERK2, include the JNK (Jun N-terminal kinase), and p38 kinases. JNKs and p38 kinases are activated in response to the pro-inflammatory cytokines TNF-alpha and interleukin-1, and by cellular stress such as heat shock, hyperosmolarity, ultraviolet radiation, lipopolysaccharides and inhibitors of protein synthesis (Derijard *et al., Cell* 1994, 76, 1025; Han *et al., Science* 1994, 265, 808; Raingeaud *et al., J Biol. Chem.* 1995, 270, 7420; Shapiro and Dinarello, *Proc. Natl. Acad. Sci. USA* 1995, 92, 12230). In contrast, ERKs are activated by mitogens and growth factors (Bokemeyer *et al., Kidney Int.* 1996, 49, 1187).

[0008] ERK2 is a widely distributed protein kinase that achieves maximum activity when both Thr183 and Tyr185 are phosphorylated by the upstream MAP kinase kinase, MEK1 (Anderson *et al., Nature* 1990, 343, 651; Crews *et al., Science* 1992, 258, 478). Upon activation, ERK2 phosphorylates many regulatory proteins, including the protein kinases Rsk90 (Bjorbaek *et al., J. Biol. Chem.* 1995, 270, 18848) and MAPKAP2 (Rouse *et al., Cell* 1994, 78, 1027), and transcription factors such as ATF2 (Raingeaud *et al., Mol. Cell Biol.* 1996, 16, 1247), Elk-1 (Raingeaud *et al., Mol. Cell Biol.* 1996, 16, 1247), c-Fos (Chen *et al., Proc. Natl. Acad. Sci. USA* 1993, 90, 10952), and c-Myc (Oliver *et al., Proc. Soc. Exp. Biol. Med.* 1995, 210, 162). ERK2 is also a downstream target of the Ras/Raf dependent pathways (Moodie *et al., Science* 1993, 260, 1658) and may help relay the signals from these potentially oncogenic proteins. ERK2 has been shown to play a role in the negative growth control of breast cancer cells (Frey and Mulder, *Cancer Res.* 1993, 57, 628) and hyperexpression of ERK2 in human breast cancer has been

reported (Sivaraman *et al.*, *J Clin. Invest.* **1997**, *99*, 1478). Activated ERK2 has also been implicated in the proliferation of endothelin-stimulated airway smooth muscle cells, suggesting a role for this kinase in asthma (Whelchel *et al.*, *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 589).

[0009] Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan *et al.*, *Chemistry & Biology* **2000**, *7*, 793-803; and Kim and Kimmel, *Curr. Opinion Genetics Dev.*, **2000** *10*, 508-514]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [PCT Application Nos.: WO 99/65897 and WO 00/38675; and Haq *et al.*, *J. Cell Biol.* **2000**, *151*, 117-130]. These diseases are associated with the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen synthase, which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β -catenin, the translation initiation factor e1F2B, as well as ATP citrate lyase, axin, heat shock factor-1, *c-Jun*, *c-myc*, *c-myb*, CREB, and CEPB α . These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation, and development.

[0010] In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein *et al.*, *PNAS* **1996**, *93*, 8455-8459; Cross *et al.*, *Biochem. J.* **1994**, *303*, 21-26); Cohen, *Biochem. Soc. Trans.* **1993**, *21*, 555-567; and Massillon *et al.*, *Biochem J.* **1994**, *299*, 123-128]. However, in a diabetic patient, where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long- term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [see, PCT Application: WO 00/38675].

Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

[0011] GSK-3 activity is also associated with Alzheimer's disease. This disease is characterized by the well-known β -amyloid peptide and the formation of intracellular neurofibrillary tangles. A β peptides are derived from the amyloid precursor protein (APP) by sequential proteolysis, catalysed by the aspartyl protease BACE2, followed by presenilin-dependent γ -secretase cleavage. It has been demonstrated that antibodies against β -amyloid plaques can slow cognitive decline in patients with Alzheimer's disease (Hock *et al.*, *Neuron*, **2003**, 38, 547-554), and thus other β -amyloid-lowering strategies (e.g., the development of agents capable of inhibiting β -amyloid peptide) would be useful in the treatment of Alzheimer's disease and other psychotic and neurodegenerative disorders. Additionally, the neurofibrillary tangles contain hyperphosphorylated Tau protein, in which Tau is phosphorylated on abnormal sites, and thus agents capable of inhibiting the hyperphosphorylation of Tau protein would be useful in the treatment of Alzheimer's disease and other psychotic and neurodegenerative disorders.

[0012] GSK-3 is known to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone *et al.*, *Current Biology* **1994**, 4, 1077-86; and Brownlee *et al.*, *Neuroreport* **1997**, 8, 3251-55]. Therefore, GSK-3 activity promotes generation of the neurofibrillary tangles and the progression of Alzheimer's disease. It has also been shown that GSK-3 facilitates APP processing and that a GSK-3 inhibitor (lithium) inhibits the generation of A β peptides through the inhibition of GSK-3 (Phiel *et al.* *Nature* **2003**, 423, 435-439). Thus, the development of inhibitors of GSK-3 would be useful for the reduction of the formation of amyloid plaques and neurofibrillary tangles, the pathological hallmarks of Alzheimer's Disease, and would also be useful for the treatment of other psychotic and neurodegenerative disorders.

[0013] Another substrate of GSK-3 is β -catenin, which is degraded after phosphorylation by GSK-3. Reduced levels of β -catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong *et al.*, *Nature* **1998**, 395, 698-702; Takashima *et al.*, *PNAS* **1993**, 90, 7789-93; and Pei *et al.*, *J. Neuropathol. Exp* **1997**, 56, 70-78].

[0014] GSK-3 activity is also associated with stroke [Wang *et al.*, *Brain Res* **2000**, 859, 381-5; Sasaki *et al.*, *Neurol Res* **2001**, 23, 588-92; Hashimoto *et al.*, *J. Biol. Chem* **2002**, 277, 32985-32991].

[0015] The AGC sub-family of kinases phosphorylate their substrates at serine and threonine residues and participate in a variety of well-known signaling processes, including, but not limited to cyclic AMP signaling, the response to insulin, apoptosis protection, diacylglycerol signaling, and control of protein translation (Peterson *et al.*, *Curr. Biol.* **1999**, 9, R521). This sub-family includes PKA, PKB (c-Akt), PKC, PRK1, 2, p70^{S6K}, and PDK.

[0016] AKT (also known as PKB or Rac-PK beta), a serine/threonine protein kinase, has been shown to be overexpressed in several types of cancer and is a mediator of normal cell functions [(Khawaja, A., *Nature* **1999**, 401, 33-34); (Yuan, Z.Q., *et al.*, *Oncogene* **2000**, 19, 2324-2330); (Namikawa, K., *et al.*, *J Neurosci.* **2000**, 20, 2875-2886,)]. AKT comprises an N-terminal pleckstrin homology (PH) domain, a kinase domain and a C-terminal "tail" region. Three isoforms of human AKT kinase (AKT-1, -2 and -3) have been reported so far [(Cheng, J.Q., *Proc. Natl. Acad. Sci. USA* **1992**, 89, 9267-9271); (Brodbeck, D. *et al.*, *J. Biol. Chem.* **1999**, 274, 9133-9136)]. The PH domain binds 3-phosphoinositides, which are synthesized by phosphatidyl inositol 3-kinase (PI3K) upon stimulation by growth factors such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor (IGF-1) [(Kulik *et al.*, *Mol. Cell. Biol.*, **1997**, 17, 1595-1606,); (Hemmings, B.A., *Science*, **1997**, 275, 628-630)]. Lipid binding to the PH domain promotes translocation of AKT to the plasma membrane and facilitates phosphorylation by another PH-domain-containing protein kinases, PDK1 at Thr308, Thr309, and Thr305 for the AKT isoforms 1, 2 and 3, respectively. A second, as of yet unknown, kinase is required for the phosphorylation of Ser473, Ser474 or Ser472 in the C-terminal tails of AKT-1, -2 and -3 respectively, in order to yield a fully activated AKT enzyme.

[0017] Once localized to the membrane, AKT mediates several functions within the cell including the metabolic effects of insulin (Calera, M.R. *et al.*, *J. Biol. Chem.* **1998**, 273, 7201-7204) induction of differentiation and/or proliferation, protein synthesis and stress responses (Alessi, D.R. *et al.*, *Curr. Opin. Genet. Dev.* **1998**, 8, 55-62,).

[0018] Manifestations of altered AKT regulation appear in both injury and disease, the most important role being in cancer. The first account of AKT was in association with human ovarian

carcinomas where expression of AKT was found to be amplified in 15% of cases (Cheng, J.Q. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, 89, 9267-9271). It has also been found to be overexpressed in 12% of pancreatic cancers (Cheng, J. Q. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, 93, 3636-3641). It was demonstrated that AKT-2 was over-expressed in 12% of ovarian carcinomas and that amplification of AKT was especially frequent in 50% of undifferentiated tumours, suggesting that AKT may also be associated with tumour aggressiveness (Bellacosa, *et al.*, *Int. J. Cancer* **1995**, 64, 280-285).

[0019] PKA (also known as cAMP-dependent protein kinase) has been shown to regulate many vital functions including energy metabolism, gene transcription, proliferation, differentiation, reproductive function, secretion, neuronal activity, memory, contractility and motility (Beebe, S.J., *Semin. Cancer Biol.* **1994**, 5, 285-294). PKA is a tetrameric holoenzyme, which contains two catalytic subunits bound to a homo-dimeric regulatory subunit (which acts to inhibit the catalytic sub-units). On binding of cAMP (enzyme activation), the catalytic subunits dissociate from the regulatory subunits to yield the active serine/threonine kinase (McKnight, G.S. *et al.*, *Recent Prog. Horm. Res.* **1988**, 44, pp. 307). Three isoforms of the catalytic subunit (C- α , C- β and C- γ) have been reported to date (Beebe, S.J. *et al.*, *J. Biol. Chem.* **1992**, 267, 25505-25512) with the C- α subunit being the most extensively studied, primarily because of its elevated expression in primary and metastatic melanomas (Becker, D. *et al.*, *Oncogene* **1990**, 5, 1133). To date, strategies to modulate the activity of the C- α subunit involve the use of antibodies, molecules that block PKA activity by targeting regulatory dimers and antisense oligonucleotides expression.

[0020] The ribosomal protein kinases p70^{S6K}-1 and -2 are also members of the AGC sub-family of protein kinases and catalyze the phosphorylation and subsequent activation of the ribosomal protein S6, which has been implicated in the translational up-regulation of mRNAs coding for the components of the protein synthetic apparatus. These mRNAs contain an oligopyrimidine tract at their 5' transcriptional start site, termed a 5'TOP, which has been shown to be essential for their regulation at the translational level (Volarevic, S. *et al.*, *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, 65, 101-186). p70^{S6K} dependent S6 phosphorylation is stimulated in response to a variety of hormones and growth factors primarily via the PI3K pathway (Coffer, P.J. *et al.*, *Biochem. Biophys. Res. Commun.*, **1994** 198, 780-786), which may be under the regulation of mTOR, since rapamycin acts to inhibit p70^{S6K} activity and blocks protein synthesis,

specifically as a result of a down-regulation of translation of these mRNA's encoding ribosomal proteins (Kuo, C.J. *et al.*, *Nature* **1992**, 358, 70-73).

[0021] *In vitro* PDK1 catalyses the phosphorylation of Thr252 in the activation loop of the p70 catalytic domain, which is indispensable for p70 activity (Alessi, D.R., *Curr. Biol.*, **1998**, 8, 69-81). The use of rapamycin and gene deletion studies of dp70S6K from *Drosophila* and p70^{S6K}1 from mouse have established the central role p70 plays in both cell growth and proliferation signaling.

[0022] The 3-phosphoinositide-dependent protein kinase-1 (PDK1) plays a key role in regulating the activity of a number of kinases belonging to the AGC subfamily of protein kinases (Alessi, D. *et al.*, *Biochem. Soc. Trans* **2001**, 29, 1). These include isoforms of protein kinase B (PKB, also known as AKT), p70 ribosomal S6 kinase (S6K) (Avruch, J. *et al.*, *Prog. Mol. Subcell. Biol.* **2001**, 26, 115), and p90 ribosomal S6 kinase (Frödin, M. *et al.*, *EMBO J.* **2000**, 19, 2924-2934). PDK1 mediated signaling is activated in response to insulin and growth factors and as a consequence of attachment of the cell to the extracellular matrix (integrin signaling). Once activated these enzymes mediate many diverse cellular events by phosphorylating key regulatory proteins that play important roles controlling processes such as cell survival, growth, proliferation and glucose regulation [(Lawlor, M.A. *et al.*, *J. Cell Sci.* **2001**, 114, 2903-2910), (Lawlor, M.A. *et al.*, *EMBO J.* **2002**, 21, 3728-3738)]. PDK1 is a 556 amino acid protein, with an N-terminal catalytic domain and a C-terminal pleckstrin homology (PH) domain, which activates its substrates by phosphorylating these kinases at their activation loop (Belham, C. *et al.*, *Curr. Biol.* **1999**, 9, R93-R96). Many human cancers including prostate and NSCL have elevated PDK1 signaling pathway function resulting from a number of distinct genetic events such as PTEN mutations or over-expression of certain key regulatory proteins [(Graff, J.R., *Expert Opin. Ther. Targets* **2002**, 6, 103-113), (Brognard, J., *et al.*, *Cancer Res.* **2001**, 61, 3986-3997)]. Inhibition of PDK1 as a potential mechanism to treat cancer was demonstrated by transfection of a PTEN negative human cancer cell line (U87MG) with antisense oligonucleotides directed against PDK1. The resulting decrease in PDK1 protein levels led to a reduction in cellular proliferation and survival (Flynn, P., *et al.*, *Curr. Biol.* **2000**, 10, 1439-1442). Consequently the design of ATP binding site inhibitors of PDK1 offers, amongst other treatments, an attractive target for cancer chemotherapy.

[0023] The diverse range of cancer cell genotypes has been attributed to the manifestation of the following six essential alterations in cell physiology: self-sufficiency in growth signaling, evasion of apoptosis, insensitivity to growth-inhibitory signaling, limitless replicative potential, sustained angiogenesis, and tissue invasion leading to metastasis (Hanahan, D. *et al.*, *Cell* **2000**, *100*, 57-70). PDK1 is a critical mediator of the PI3K signalling pathway, which regulates a multitude of cellular function including growth, proliferation and survival. Consequently, inhibition of this pathway could affect four or more of the six defining requirements for cancer progression. As such it is anticipated that a PDK1 inhibitor will have an effect on the growth of a very wide range of human cancers.

[0024] Specifically, increased levels of PI3K pathway activity has been directly associated with the development of a number of human cancers, progression to an aggressive refractory state (acquired resistance to chemotherapies) and poor prognosis. This increased activity has been attributed to a series of key events including decreased activity of negative pathway regulators such as the phosphatase PTEN, activating mutations of positive pathway regulators such as Ras, and overexpression of components of the pathway itself such as PKB, examples include: brain (gliomas), breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, thyroid [(Teng, D.H. *et al.*, *Cancer Res.*, **1997** *57*, 5221-5225), (Brognard, J. *et al.*, *Cancer Res.*, **2001**, *61*, 3986-3997), (Cheng, J.Q. *et al.*, *Proc. Natl. Acad. Sci.* **1996**, *93*, 3636-3641), (*Int. J. Cancer* **1995**, *64*, 280), (Graff, J.R., *Expert Opin. Ther. Targets* **2002**, *6*, 103-113), (*Am. J. Pathol.* **2001**, *159*, 431)].

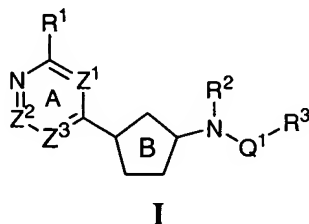
[0025] Additionally, decreased pathway function through gene knockout, gene knockdown, dominant negative studies, and small molecule inhibitors of the pathway have been demonstrated to reverse many of the cancer phenotypes *in vitro* (some studies have also demonstrated a similar effect *in vivo*) such as block proliferation, reduce viability and sensitize cancer cells to known chemotherapies in a series of cell lines, representing the following cancers: pancreatic [(Cheng, J.Q. *et al.*, *Proc. Natl. Acad. Sci.* **1996**, *93*, 3636-3641), (*Neoplasia* **2001**, *3*, 278)], lung [(Brognard, J. *et al.*, *Cancer Res.* **2001**, *61*, 3986-3997), (*Neoplasia* **2001**, *3*, 278)], ovarian [(Hayakawa, J. *et al.*, *Cancer Res.* **2000**, *60*, 5988-5994), (*Neoplasia* **2001**, *3*, 278)], breast (*Mol. Cancer Ther.* **2002**, *1*, 707), colon [(*Neoplasia* **2001**, *3*, 278), (Arico, S. *et al.*, *J. Biol. Chem.* **2002**, *277*, 27613-27621)], cervical (*Neoplasia* **2001**, *3*, 278), prostate [(*Endocrinology* **2001**, *142*, 4795), (Thakkar, H. *et al. J. Biol. Chem.* **2001**, *276*, 38361-38369),

(Chen, X. *et al.*, *Oncogene* **2001**, 20, 6073-6083)] and brain (glioblastomas) [(Flynn, P. *et al.*, *Curr. Biol.* **2000**, 10, 1439-1442)].

[0026] Accordingly, there is a great need to develop inhibitors of ROCK, ERK, GSK, and members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) that would be useful in treating various diseases or conditions associated with ROCK, ERK or GSK activation, or activation of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB), particularly given the inadequate treatments currently available for the majority of these disorders.

SUMMARY OF THE INVENTION

[0027] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of ROCK, ERK, GSK, and members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB). These compounds have the general formula I:



or a pharmaceutically acceptable derivative thereof, wherein ring B, R¹, R², R³, Z¹, Z², Z³, and Q¹ are as defined below.

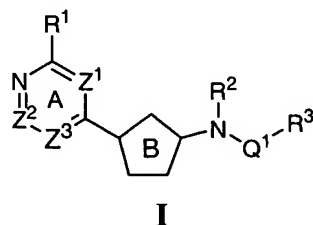
[0028] These compounds, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of disorders, including allergic disorders such as asthma and atopic dermatitis, autoimmune diseases such as SLE lupus and psoriasis, conditions associated with organ transplantation, proliferative disorders such as cancer, inflammatory diseases, destructive bone disorders, hypertension, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, arteriosclerosis, spasm, retinopathy, erectile dysfunction (ED), Alzheimer's Disease, reperfusion/ischemia induced injury (e.g., stroke), and AIDS, to name a few.

[0029] The compounds provided by this invention are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases, and the comparative evaluation of new kinase inhibitors.

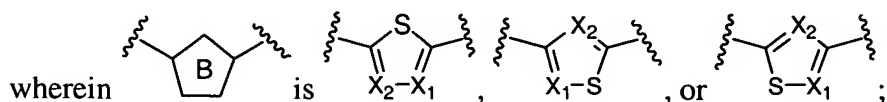
DETAILED DESCRIPTION OF THE INVENTION

[0030] I. General Description of Compounds of the Invention:

[0031] The present invention relates to a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:



R^1 is halogen, CN, NO_2 , or V_mR ;

Z^1 and Z^3 are each independently N or CR^Z , and Z^2 is N or CR^1 , provided that Z^1 , Z^2 and Z^3 are not simultaneously N;

each occurrence of R^Z is independently halogen, CN, NO_2 , or $\text{U}_n\text{R}'$;

R^2 is $\text{U}_n\text{R}'$;

X^1 and X^2 are each independently CR^4 or N;

each occurrence of R^4 is independently halogen, CN, NO_2 , or V_mR ;

each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by –NR–, –S–, –O–, –CS–, – CO_2 –, –OCO–, –CO–, –COCO–, –CONR–, –NRCO–, – NRCO_2 –, – SO_2NR –, – NRSO_2 –, –CONRNR–, –NRCONR–, –OCONR–, –NRNR–, – NRSO_2NR –, –SO–, – SO_2 –, –PO–, – PO_2 –, or –POR–;

m and n are each independently 0 or 1;

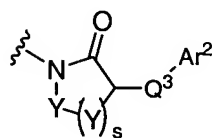
each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic

ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q¹ is -CO-, -SO₂-, -CONR-, or -SO₂NR-;

R³ is Q²-Ar¹,

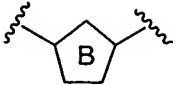
or R² and Q¹-R³, taken together with the nitrogen atom, form the cyclic group:

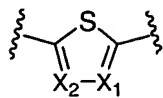


, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO₂-, -O-, -S-, -NR⁵-, or -C(R⁵)₂-, and R⁵ is U_nR';

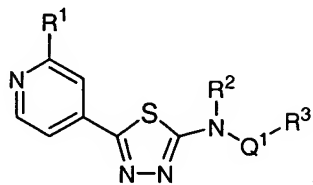
Q² and Q³ are each independently a bond or a C₁₋₆ alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by -NR'-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, -NR'CO₂-, -SO₂NR'-, -NR'SO₂-, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, -NR'SO₂NR'-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R⁶, wherein each occurrence of R⁶ is independently halogen, CN, NO₂, or U_nR', or two occurrences of R⁶, or R' and R⁶, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar¹ and Ar² are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ and Ar² are each optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁-C₆ alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R⁷ is independently R', halogen, NO₂, or CN.

[0032] In certain embodiments, for compounds described where  is



, one or more of, or all of the following conditions apply:



A) for compounds having the structure:

i) when R^1 is Cl, and R^2 is $-\text{CH}(\text{CH}_3)\text{COOCH}_3$ or hydrogen, then $Q^1\text{-}R^3$ is not $-\text{CO}(\text{unsubstituted phenyl})$, $-\text{CO}(\text{unsubstituted 2-furyl})$, or $-\text{COCH}_2(\text{unsubstituted phenyl})$;

ii) when R^1 is hydrogen, R^2 is hydrogen, and Q^1 is $-\text{CO}-$, then R^3 is not:

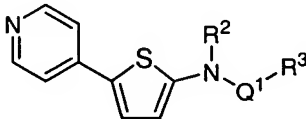
- a) phenyl substituted with $4\text{-O}(\text{CH}_2)_{4-7}\text{CH}_3$ or $4\text{-(CH}_2)_{4-7}\text{CH}_3$;
- b) phenyl substituted with 2-Cl, 4- NO_2 , 4-Cl, 2-Br, 3-Br, 3-I, 3- CH_3 , 4- OCH_3 , 3- NO_2 , or 4-I;
- c) 2,6- OCH_3 -phenyl
- d) (5-Cl, 3- CH_3 , 1-phenyl)-pyrazol-4-yl; or
- e) 4-OnBu-phenyl, $-\text{CH}_2\text{O}(2\text{-F-phenyl})$, $-(\text{CH}_2)_2\text{phenyl}$, furan-2-yl, thiophen-2-yl, 4- CH_3 -phenyl, $-\text{CH}_2\text{O}(2\text{-CH}_3\text{-phenyl})$, 3- OCH_3 -phenyl, 2-(2,5-dimethoxyphenyl)quinolin-4-yl, $-\text{NH}(4\text{-Cl-phenyl})$, $-\text{NH}(3,4\text{-dichlorophenyl})$, (2- CO_2H , 3- NO_2)-phenyl, 3,5-dimethyl-1,2,4-oxazol-4-yl, $-\text{CH}=\text{CH}$ -phenyl, 4-F-phenyl, $\text{C}(\text{CH}_3)_2\text{O}(4\text{-Cl-phenyl})$, $-\text{NH}(3\text{-Cl-phenyl})$, $-\text{NHphenyl}$, unsubstituted phenyl, 3,4,5- OCH_3 -phenyl, 4- NO_2 -phenyl, 4-cyclopentoxy-phenyl, $-(\text{CH}_2)_3\text{phenyl}$, $-(\text{tricyclo}[3.3.1.1^{3,7}]\text{decan-1-yl})$, $-\text{CH}_2\text{O}(3\text{-CH}_3\text{-phenyl})$, 3- NO_2 -phenyl, $-\text{cyclopropyl}(4\text{-tert-butyl-phenyl})$, 2,3- OCH_3 -phenyl, 1,3-benzodioxo-5-yl, $-\text{CH}_2\text{-O}(4\text{-F-phenyl})$, or 3-Br-phenyl;

iii) when R^1 is hydrogen, R^2 is hydrogen, and Q^1 is $-\text{CSNH}-$, then R^3 is not 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl;

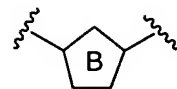
iv) when R^1 is hydrogen, R^2 is hydrogen, and Q^1 is SO_2 , then R^3 is not unsubstituted phenyl, unsubstituted benzyl, unsubstituted naphthyl, phenyl substituted with para- $NHCOCH_3$, para- NH_2 , or para- CH_3 ; and

v) when R^1 is hydrogen, R^2 is $-CH_2CH=CH_2$, and Q^1 is CO , then R^3 is not 4- OCH_3 -phenyl, unsubstituted naphthyl, $-NH-(4-OCH_3\text{-phenyl})$, 3,5- OCH_3 -phenyl, $-CH_2O$ phenyl, $-CH_2$ -thiophen-2-yl, or $-CH(phenyl)(CH_2CH_3)$; and

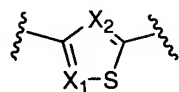
vi) when R^1 is hydrogen, R^2 is CH_2CH_3 , and Q^1 is CO , then R^3 is not 2,4- Cl -phenyl; and

B) for compounds having the structure: , when R^2 is hydrogen or CH^3 , and Q^1 is $-CO-$, then R^3 is not $-OCH_2CH_2OCH_2$ phenyl.

[0033] In certain other embodiments, for compounds described where

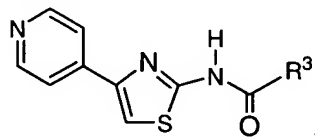


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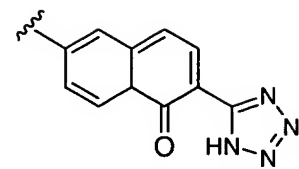


, one or more of, or all of the following conditions apply:

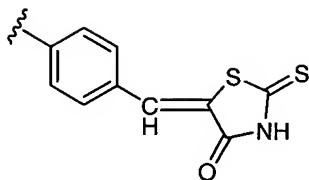
A) for compounds having the structure:



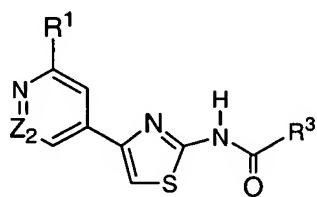
i) when R^3 is Q^2-Ar^1 , and Q^2 is a bond then Ar^1 is not any one or more of the following: unsubstituted phenyl or phenyl substituted with 2-Br; 2-Cl; 2-I; 2,6-F; 3,5- OCH_3 ; 3,4,5- OCH_3 ; 2,4- OCH_3 ; 3,4- CH_3 ; 2,5- Cl ; 3,4- OCH_3 ; 2- Cl , 5- NO_2 ; 3,5- Cl ; 3- $O(CH_2)_4CH_3$, 3-O-n-butyl, 3- CF_3 , 3- OCH_3 , 3-Br; 3- NO_2 ; 3- CH_3 ; 3-O-phenyl; 3- Cl ; 4- $N(CH_3)_2$; 4- $N(CH_2CH_3)_2$; 4- $SO_2N(R')_2$; 4-CN; 4- $COOCH_3$; 4-C(O)phenyl; 4-phenyl; 4-tert-butyl, 4-O-phenyl; 4-O-isopropyl; 4- OCH_3 ; 4- OCH_2CH_3 ; 4-O-n-butyl; 4- Cl ; 4-Br; 4-F; 4- CH_3 ; 4- NO_2 ; 4- Cl ; 3- NO_2 , 4-morpholino; 3- NO_2 , 2,5-dioxopyrrolidinyl, or 4-piperidinyl; and



ii) R^3 is not any one or more of the following groups:



, $-\text{CH}=\text{CH}(\text{thiophen-2-yl})$, $-\text{CH}=\text{CH}$ -unsubstituted phenyl, $-\text{CH}_2(3\text{-NHCOPh-phenyl})$, $-\text{6-bromo-2-(4-ethylphenyl)-4-quinolinyl}$, $-\text{CH}_2\text{-pyrrolidine}$, unsubstituted cyclohexyl, unsubstituted benzyl, unsubstituted furan-2-yl, $-\text{CH}=\text{CH}(3\text{-NO}_2\text{-phenyl})$, $-\text{CH}=\text{CH}(4\text{-NO}_2\text{-phenyl})$, $-\text{CH}_2\text{-naphthyl}$, unsubstituted naphthyl, unsubstituted thiophene, unsubstituted cyclopropyl, 1,4-benzodioxin, 2-oxo-1-benzopyran, 4-oxo-1-benzopyran, 2-thienyl-quinolin-4-yl, 3-chloro-benzo[b]thiophen-2-yl, 5-Br-(thiophen-2-yl), 5-Cl-(thiophen-2-yl), 5- NO_2 -(thiophen-2-yl), 5- NO_2 -(furan-2-yl), 2,5-Cl-(thiophen-3-yl), $-\text{CH}=\text{CH}-(5\text{-NO}_2\text{-thiophen-2-yl})$, 5- NO_2 -(benzothiophen-2-yl), 3- OCH_3 -(naphth-2-yl), $-\text{CH}_2\text{O}(2,4\text{-Cl-phenyl})$, $-(\text{CH}_2)_2\text{S-phenyl}$, 2-phenyl-quinolin-4-yl, $-\text{CH}_2\text{O}(4\text{-Cl-phenyl})$, $-\text{CH}_2\text{CH}_2\text{-3-(4-Cl-phenyl)-1-phenyl-1-H-pyrazol-4-yl}$, or $-\text{CH}_2(1,3\text{-dioxoisindole})$; and



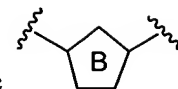
B) for compounds having the structure:

i) when R^1 is Cl, and X_1 is C-Cl, then R^3 is not $\text{NHSO}_2\text{-(2-CF}_3\text{-phenyl)}$ or $-\text{NHSO}_2\text{-(2,6-dimethoxy-phenyl)}$;

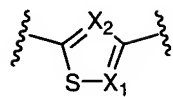
ii) when R^1 is CH_3 , and X_1 is C- CH_3 , then R^3 is not an optionally substituted indole or optionally substituted dihydroindole; and

C) for compounds of general formula I, when Z_1 , Z_2 and Z_3 are each CH, R^1 is H, X^1 is CH and X_2 is C- COOCH_3 , then R^3 is not 2-(4-ethyl-phenyl)-6-bromo-quinolin-4-yl.

[0034] In yet other embodiments, for compounds described above where

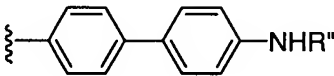


is



, one or more of, or all of the following conditions apply:

A) when Z^1 , Z^2 and Z^3 are each CH, X^2 is N, X^1 is CH, Q^1 is $-\text{CONR}-$, and R^2 is hydrogen or $-\text{CH}_3$, then R^3 is not optionally substituted pyridyl, optionally substituted thiazol-4-yl, $-\text{CH}_2\text{pyridyl}$, benzimidazol-4-yl, quinolin-2-yl, 1-bromo-isoquinolin-3-yl, benzthiazol-2-yl, optionally substituted 5,6,7,8-tetrahydro-naphthyridin-2-yl, or phenyl substituted with $-\text{CH}_2\text{piperidiny}$; and

B) when Z^1 , Z^2 and Z^3 are each CH, X^2 is N, X^1 is CH, Q^1 is SO_2 , and R^2 is hydrogen, then R^3 is not phenyl substituted with  where R'' is hydrogen or $-\text{COCH}_3$;

C) when Z^1 , Z^2 and Z^3 are each CH, X_1 is $\text{C}-\text{CO}_2\text{H}$, X^2 is CH, R^2 is hydrogen, and Q^1 is SO_2 , then R^3 is not 2- CH_3 -phenyl;

D) when Z^1 , Z^2 and Z^3 are each CH, X_1 is CH, X^2 is N, R^2 is hydrogen, and Q^1 is CO, then R^3 is not 5-methoxy-6-trifluoromethyl-1H-indole.

[0035] 2. Compounds and Definitions:

[0036] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0037] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase

“optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted”, whether preceded by the term “optionally” or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0038] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0039] The term “heteroaliphatic”, as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” groups.

[0040] The term “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0041] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidiny) or NR⁺ (as in N-substituted pyrrolidiny)).

[0042] The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

[0043] The term “alkoxy”, or “thioalkyl”, as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0044] The terms “haloalkyl”, “haloalkenyl” and “haloalkoxy” means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br, or I.

[0045] The term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring”. The term “aryl” also refers to heteroaryl ring systems as defined hereinbelow.

[0046] The term “heteroaryl”, used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy”, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic”.

[0047] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be “optionally substituted”. Unless otherwise defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; R° ; $-OR^\circ$; $-SR^\circ$; phenyl (Ph) optionally substituted with R° ; $-O(Ph)$ optionally substituted with R° ; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R° ; $-CH=CH(Ph)$, optionally substituted with R° ; $-NO_2$; $-CN$; $-N(R^\circ)_2$; $-NR^\circ C(O)R^\circ$; $-NR^\circ C(S)R^\circ$; $-NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ C(S)N(R^\circ)_2$; $-NR^\circ CO_2R^\circ$; $-NR^\circ NR^\circ C(O)R^\circ$; $-NR^\circ NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ NR^\circ CO_2R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-CO_2R^\circ$; $-C(O)R^\circ$; $-C(S)R^\circ$; $-C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-OC(O)N(R^\circ)_2$; $-OC(O)R^\circ$; $-C(O)N(OR^\circ)R^\circ$; $-C(NOR^\circ)R^\circ$; $-S(O)_2R^\circ$; $-S(O)_3R^\circ$; $-SO_2N(R^\circ)_2$; $-S(O)R^\circ$; $-NR^\circ SO_2N(R^\circ)_2$; $-NR^\circ SO_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(=NH)-N(R^\circ)_2$; $-P(O)_2R^\circ$; $-PO(R^\circ)_2$; $-OPO(R^\circ)_2$; $-(CH_2)_{0-2}NHC(O)R^\circ$; phenyl (Ph) optionally substituted with R° ; $-O(Ph)$ optionally substituted with R° ; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R° ; or $-CH=CH(Ph)$, optionally substituted with R° ; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, $-O(Ph)$, or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of R° , on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0048] . Optional substituents on the aliphatic group of R° are selected from NH_2 , $NH(C_{1-4}aliphatic)$, $N(C_{1-4}aliphatic)_2$, halogen, $C_{1-4}aliphatic$, OH , $O(C_{1-4}aliphatic)$, NO_2 , CN , CO_2H , $CO_2(C_{1-4}aliphatic)$, $O(haloC_{1-4}aliphatic)$, or $haloC_{1-4}aliphatic$, wherein each of the foregoing $C_{1-4}aliphatic$ groups of R° is unsubstituted.

[0049] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be “optionally substituted”. Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR^{*}, =NN(R^{*})₂, =NNHC(O)R^{*}, =NNHCO₂(alkyl), =NNHSO₂(alkyl), or =NR^{*}, where each R^{*} is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group.

[0050] Unless otherwise defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from -R⁺, -N(R⁺)₂, -C(O)R⁺, -CO₂R⁺, -C(O)C(O)R⁺, -C(O)CH₂C(O)R⁺, -SO₂R⁺, -SO₂N(R⁺)₂, -C(=S)N(R⁺)₂, -C(=NH)-N(R⁺)₂, or -NR⁺SO₂R⁺; wherein R⁺ is hydrogen, an optionally substituted C₁₋₆ aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH₂(Ph), optionally substituted -(CH₂)₁₋₂(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R⁺, on the same substituent or different substituents, taken together with the atom(s) to which each R⁺ group is bound, form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

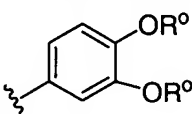
[0051] Optional substituents on the aliphatic group or the phenyl ring of R⁺ are selected from -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, halogen, C₁₋₄ aliphatic, -OH, -O(C₁₋₄ aliphatic), -NO₂, -CN, -CO₂H, -CO₂(C₁₋₄ aliphatic), -O(halo C₁₋₄ aliphatic), or halo(C₁₋₄ aliphatic), wherein each of the foregoing C₁₋₄aliphatic groups of R⁺ is unsubstituted.

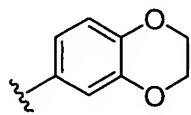
[0052] The term “alkylidene chain” refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0053] As detailed above, in some embodiments, two independent occurrences of R^o (or R⁺, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially

unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0054] Exemplary rings that are formed when two independent occurrences of R^o (or R^+ , R , R' or any other variable similarly defined herein), are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+ , R , R' or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+ , R , R' or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted

with two occurrences of OR^o , these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



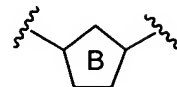
. It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+ , R , R' or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0055] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within

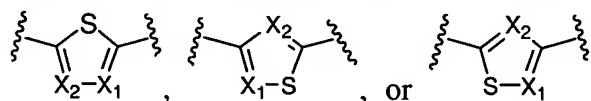
the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0056] 3. *Description of Exemplary Compounds:*

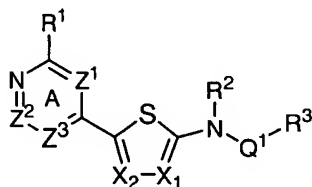
[0057] As described generally above for compounds of formula I,



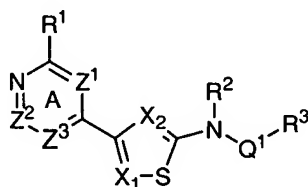
is



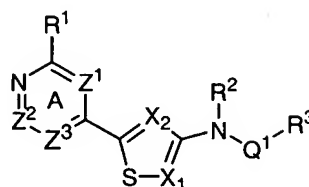
Thus, in certain embodiments, compounds of formula **I-A**, **I-B**, or **I-C** are provided:



I-A



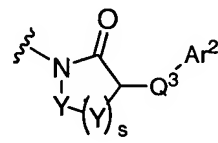
I-B



I-C

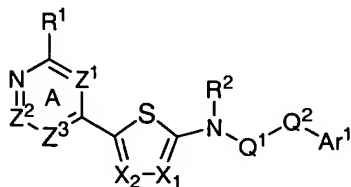
[0058] As also described generally above for compounds of formula I, R^3 is Q^2-Ar^1 , or R^2

and Q^1-R^3 , taken together with the nitrogen atom, form the cyclic group:

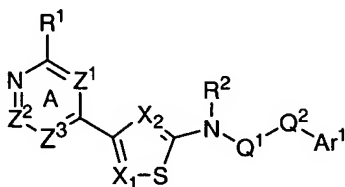


, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, $-CO-$, $-CS-$, $-SO_2-$, $-O-$, $-S-$, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR' .

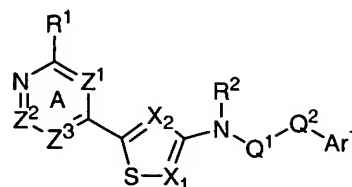
[0059] Accordingly, in one embodiment, R^3 is Q^2-Ar^1 and compounds of formula **I-A-i**, **I-B-i**, and **I-C-i** are provided.



I-A-i



I-B-i



I-C-i

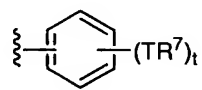
[0060] In general, for compounds of formula **I** (and compounds of formula **I-A-i**, **I-B-i**, and **I-C-i**), R^2 is U_nR' . In certain embodiments, R^2 is hydrogen, or is U_nR' , where n is 1, and U is a C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by $-O-$, $-NR-$, $-S-$, or $-CO-$. In other embodiments, U is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NR-$, $-CH_2CH_2O-$, $-CH_2CH_2S-$, $-CH_2CH_2NR-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2NR-$, $-CH_2CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2CH_2NR-$, $-CH_2CH_2OCH_2CH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_3NHCH_2CH_2-$, or $-CH_2CH_2NHCH_2CH_2-$, and exemplary R' groups are hydrogen, C_1 - C_4 alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R' , taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered saturated, partially unsaturated, or unsaturated heterocyclyl ring.

[0061] As described generally above, for compounds of formula **I** (and compounds of formula **I-A-i**, **I-B-i**, and **I-C-i**), Q^1 is $-CO-$, $-SO_2-$, $-CONR-$, or $-SO_2NR-$. In some embodiments, Q^1 is $-CO-$ or $-SO_2NR-$. In other embodiments, Q^1 is $-CO-$.

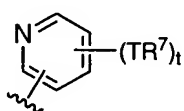
[0062] For compounds of general formula **I** (and compounds of formula **I-A-i**, **I-B-i**, and **I-C-i**), Q^2 is a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-CS-$, $-CO_2-$, $-OCO-$, $-CO-$, $-COCO-$, $-CONR'-$, $-NR'CO-$, $-NR'CO_2-$, $-SO_2NR'-$, $-NR'SO_2-$, $-CONR'NR'-$, $-NR'CONR'-$, $-OCONR'-$, $-NR'NR'-$, $-NR'SO_2NR'-$, $-SO-$, $-SO_2-$, $-PO-$, $-PO_2-$, or $-POR'-$; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, CN , NO_2 , or U_nR' , or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring. In some embodiments, Q^2 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3. In certain other embodiments, R^6 is R' , $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-OR'$, $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. Examples of such R^6 groups include, but are not limited to CH_2OH , CH_2CH_2OH , OH , OMe , OEt , NH_2 ,

NH(Me), NH(Et), N(Me)(Me), CH₂NH₂, CH₂CH₂NH₂, NHCO₂*t*-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, NH(CH₂)₃NH₂, NH(CH₂)₂NH₂, NH(CH₂)₂NHEt, NHCH₂pyridyl, NHSO₂phenyl, NHC(O)CH₂C(O)O*t*-butyl, NHC(O)CH₂NH₃, and NHCH₂-imidazol-4-yl.

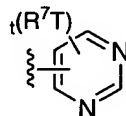
[0063] In certain exemplary embodiments, Ar¹ groups are:



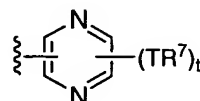
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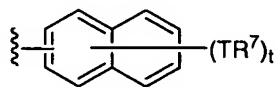
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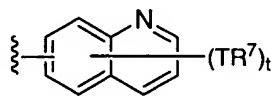
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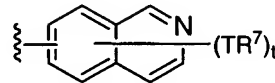
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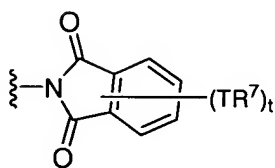
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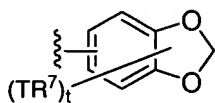
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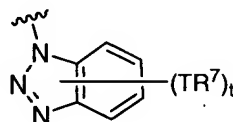
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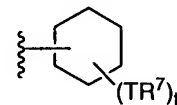
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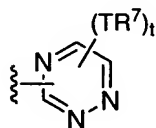
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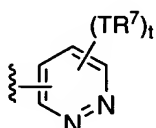
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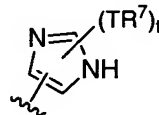
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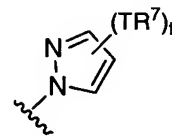
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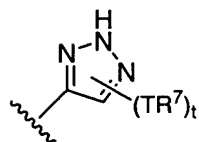
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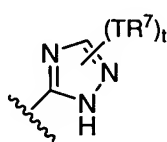
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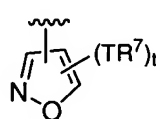
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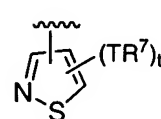
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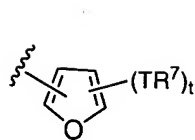
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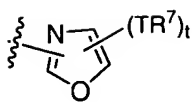
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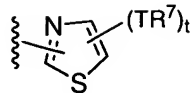
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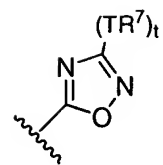
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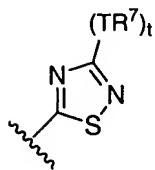
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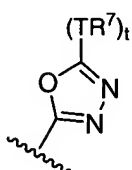
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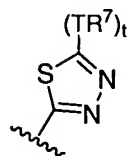
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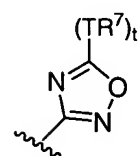
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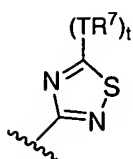
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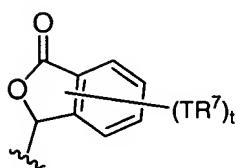
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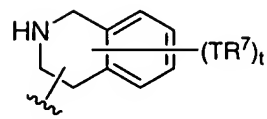
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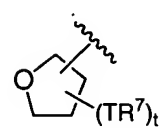
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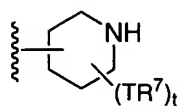
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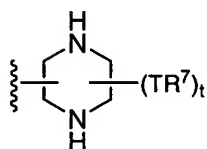
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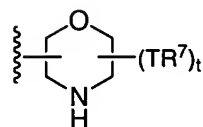
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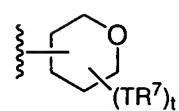
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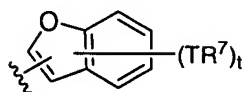
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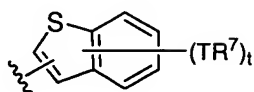
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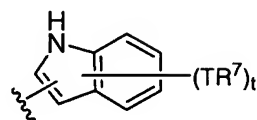
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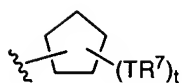
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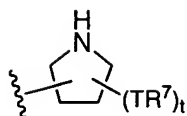
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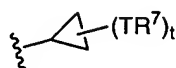
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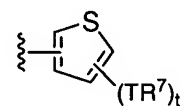
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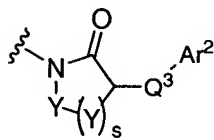


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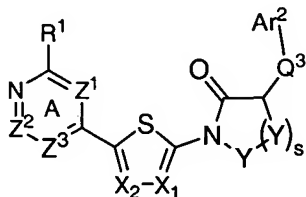
wherein t is 0, 1, 2, 3, 4 or 5, and wherein any Ar¹ is bonded to Q² through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR⁷, wherein TR⁷ is defined generally above.

[0064] In other embodiments, Ar¹ is **a, b, e, g, h, i, j, k, r, cc, dd, ff, jj, ll, or pp**. As described generally above, Ar¹ is optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁-C₆ alkylidene chain wherein up to two methylene units of T are optionally replaced by -NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R⁷ is independently R', halogen, NO₂, or CN. In certain embodiments, T is a bond or is an optionally substituted C₁₋₆ alkylidene chain wherein one or two methylene units are optionally and independently replaced by -O-, -NR-, -S-, -SO₂-, -COO-, -CO-, -OSO₂-, -NRSO₂-, -CONR-, or -SO₂NR-, and R⁷ is R' or halogen. In other embodiments, each occurrence of TR⁷ is independently -C₁₋₃alkyl, -OR', -SR', -CF₃, -OCF₃, -SCF₃, -F, -Cl, I, -Br, -COOR', -COR', -O(CH₂)₄N(R)(R'), -O(CH₂)₃N(R)(R'), -O(CH₂)₂N(R)(R'), -O(CH₂)N(R)(R'), -O(CH₂)₄CON(R)(R'), -O(CH₂)₃CON(R)(R'), -O(CH₂)₂CON(R)(R'), -O(CH₂)CON(R)(R'), -C(O)N(R)(R'), -(CH₂)₄OR', -(CH₂)₃OR', -(CH₂)₂OR', -CH₂OR', optionally substituted phenyl or benzyl, -N(R)(R'), -(CH₂)₄N(R)(R'), -(CH₂)₃N(R)(R'), -(CH₂)₂N(R)(R'), -(CH₂)N(R)(R'), or SO₂N(R)(R'), NRSO₂R', CON(R)(R'), or -OSO₂R', where, as defined generally above, each occurrence of R is independently hydrogen or an optionally substituted C₁₋₆ aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C₁₋₆ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

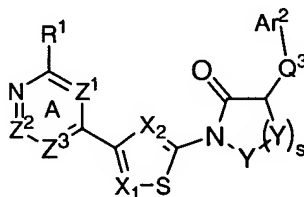
[0065] In another embodiment, R^3 is Q^2-Ar^1 , or R^2 and Q^1-R^3 , taken together with the



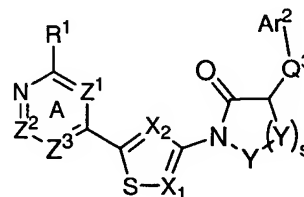
nitrogen atom, form the cyclic group: , where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, $-CO-$, $-CS-$, $-SO_2-$, $-O-$, $-S-$, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR' , and compounds of formula **I-A-ii**, **I-B-ii**, and **I-C-ii** are provided:



I-A-ii



I-B-ii

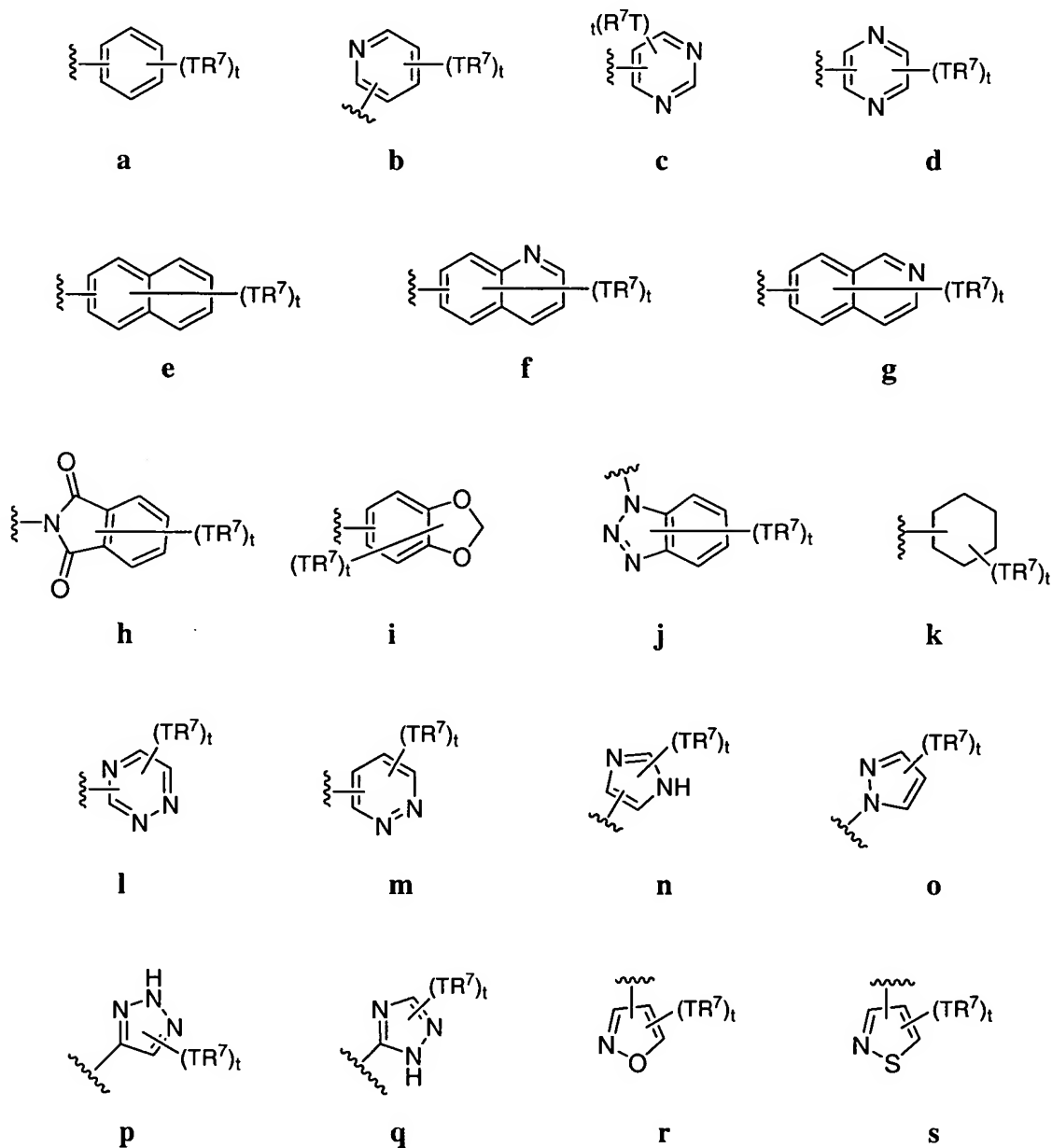


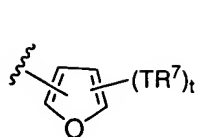
I-C-ii

[0066] For compounds of formula **I-A-ii**, **I-B-ii**, and **I-C-ii**, Q^3 is a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-CS-$, $-CO_2-$, $-OCO-$, $-CO-$, $-COCO-$, $-CONR'-$, $-NR'CO-$, $-NR'CO_2-$, $-SO_2NR'-$, $-NR'SO_2-$, $-CONR'NR'-$, $-NR'CONR'-$, $-OCONR'-$, $-NR'NR'-$, $-NR'SO_2NR'-$, $-SO-$, $-SO_2-$, $-PO-$, $-PO_2-$, or $-POR'-$; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, CN , NO_2 , or U_nR' , or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring. In some embodiments, Q^3 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3. In certain other embodiments, R^6 is R' , $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-OR'$, $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. Examples of such R^6 groups include, but are not limited to CH_2OH , CH_2CH_2OH , OH , OMe , OEt , NH_2 , $NH(Me)$, $NH(Et)$, $N(Me)(Me)$, CH_2NH_2 , $CH_2CH_2NH_2$, $NHCO_2t$ -butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl,

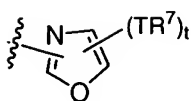
NH(CH₂)₃NH₂, NH(CH₂)₂NH₂, NH(CH₂)₂NHEt, NHCH₂pyridyl, NHSO₂phenyl, NHC(O)CH₂C(O)Ot-butyl, NHC(O)CH₂NH₃, and NHCH₂-imidazol-4-yl.

[0067] For compounds of general formula **I-A-ii**, **I-B-ii**, and **I-C-ii**, exemplary Ar² groups are:

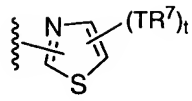




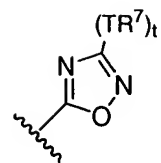
t



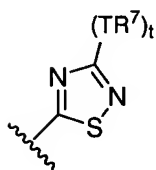
u



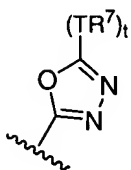
v



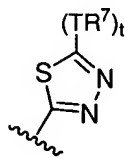
w



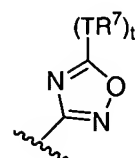
x



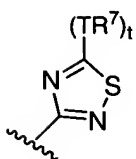
y



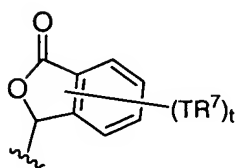
z



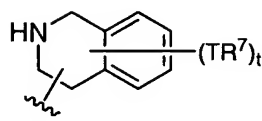
aa



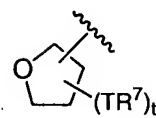
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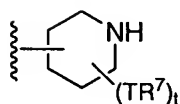
cc



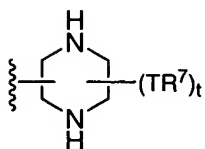
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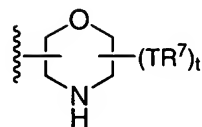
ee



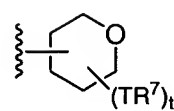
ff



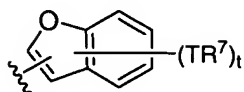
gg



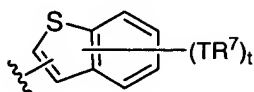
hh



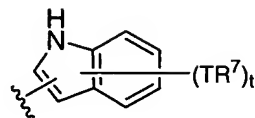
ii



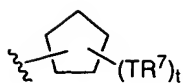
jj



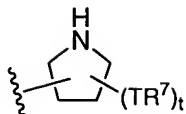
kk



ll



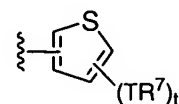
mm



nn



oo



pp

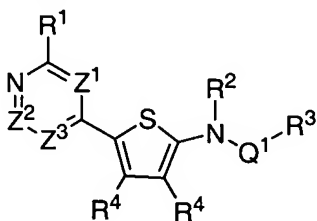
wherein t is 0, 1, 2, 3, 4 or 5, and wherein any Ar² is bonded to Q³ through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR⁷, wherein TR⁷ is defined generally above.

[0068] In more preferred embodiments, Ar² is **a, b, e, g, h, i, j, k, n, r, cc, dd, ff, jj, ll, or pp**.

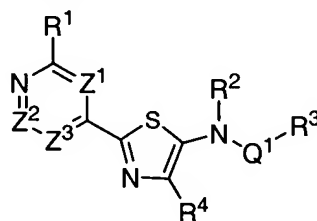
[0069] As described generally above, Ar² is optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁-C₆ alkylidene chain wherein up to two methylene units of T are optionally replaced by -NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R⁷ is independently R', halogen, NO₂, or CN. In certain embodiments, T is a bond or is an optionally substituted C₁₋₆ alkylidene chain wherein one or two methylene units are optionally and independently replaced by -O-, -NR-, -S-, -SO₂-, -COO-, -CO-, -OSO₂-, -NRSO₂-, -CONR-, or -SO₂NR-, and R⁷ is R' or halogen. In other embodiments, each occurrence of TR⁷ is independently -C₁₋₃alkyl, -OR', -SR', -CF₃, -OCF₃, -SCF₃, -F, -Cl, I, -Br, -COOR', -COR', -O(CH₂)₄N(R)(R'), -O(CH₂)₃N(R)(R'), -O(CH₂)₂N(R)(R'), -O(CH₂)N(R)(R'), -O(CH₂)₄CON(R)(R'), -O(CH₂)₃CON(R)(R'), -O(CH₂)₂CON(R)(R'), -O(CH₂)CON(R)(R'), -C(O)N(R)(R'), -(CH₂)₄OR', -(CH₂)₃OR', -(CH₂)₂OR', -CH₂OR', optionally substituted phenyl or benzyl, -N(R)(R'), -(CH₂)₄N(R)(R'), -(CH₂)₃N(R)(R'), -(CH₂)₂N(R)(R'), -(CH₂)N(R)(R'), or SO₂N(R)(R'), NRSO₂R', CON(R)(R'), or -OSO₂R', where, as defined generally above, each occurrence of R is independently hydrogen or an optionally substituted C₁₋₆ aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C₁₋₆ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0070] In certain embodiments, for compounds of formula **I-b**, R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic.

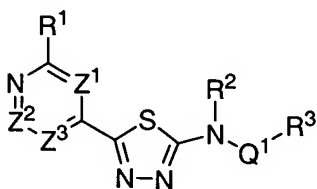
[0071] As described generally above, for compounds of formula **I**, **I-A-i**, **I-B-i**, **I-C-i**, **I-A-ii**, **I-B-ii**, and **I-C-ii**, X^1 and X^2 are each independently CR^4 or N, and thus compounds of formulas **II**, **III**, **IV**, **V**, **VI**, **VII**, **VIII**, **IX**, **X**, **XI**, **XII**, and **XIII** are provided:



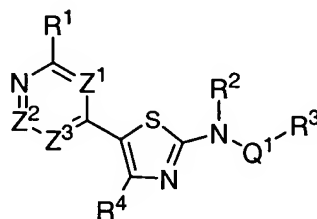
II



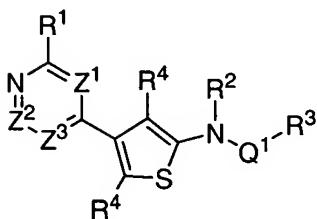
III



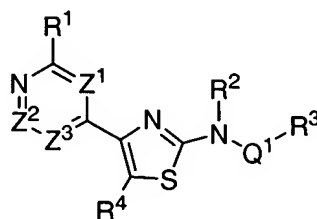
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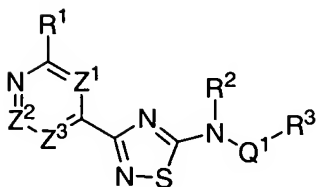
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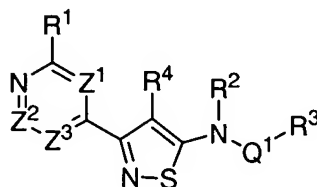
VI



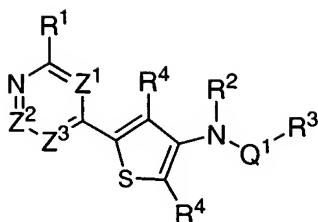
VII



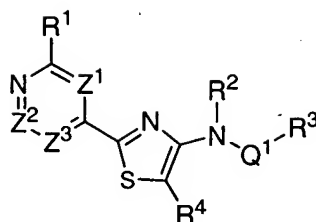
VIII



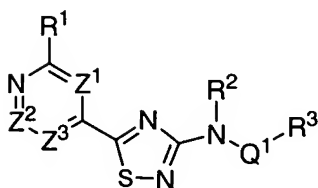
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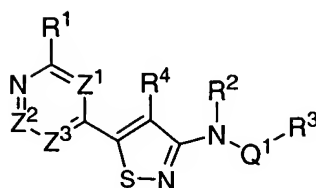
X



XI

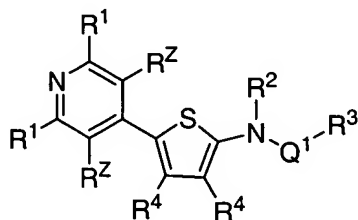


XII

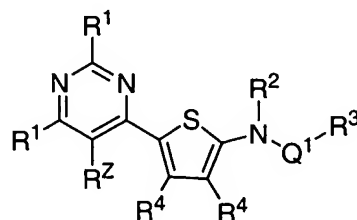


XIII

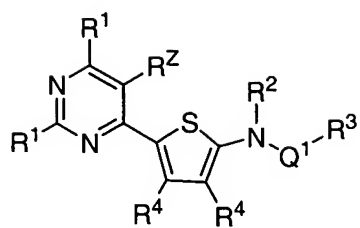
[0072] In certain embodiments, for compounds of formula **I**, **I-A-i**, **I-B-i**, **I-C-i**, **I-A-ii**, **I-B-ii**, and **I-C-ii**, ring A is a pyridyl, pyrimidinyl, triazinyl, or pyridazinyl group. Accordingly, in certain embodiments, compounds have one of the structures of formulas **II-A**, **II-B**, **II-C**, **II-D**, **II-E**, **II-F**, **III-A**, **III-B**, **III-C**, **III-D**, **III-E**, **III-F**, **IV-A**, **IV-B**, **IV-C**, **IV-D**, **IV-E**, **IV-F**, **V-A**, **V-B**, **V-C**, **V-D**, **V-E**, **V-F**, **VI-A**, **VI-B**, **VI-C**, **VI-D**, **VI-E**, **VI-F**, **VII-A**, **VII-B**, **VII-C**, **VII-D**, **VII-E**, **VII-F**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **IX-A**, **IX-B**, **IX-C**, **IX-D**, **IX-E**, **IX-F**, **X-A**, **X-B**, **X-C**, **X-D**, **X-E**, **X-F**, **XI-A**, **XI-B**, **XI-C**, **XI-D**, **XI-E**, **XI-F**, **XII-A**, **XII-B**, **XII-C**, **XII-D**, **XII-E**, **XII-F**, **XIII-A**, **XIII-B**, **XIII-C**, **XIII-D**, **XIII-E**, and **XIII-F** depicted below:



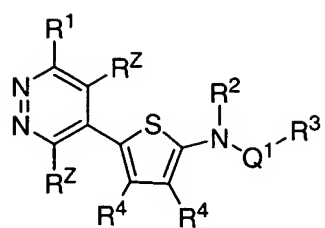
II-A



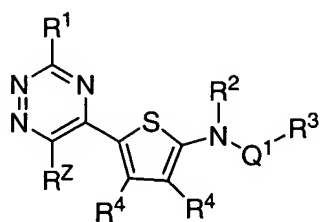
II-B



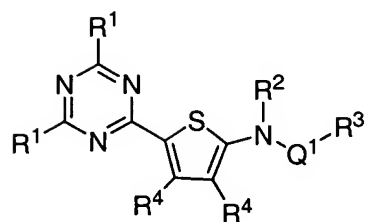
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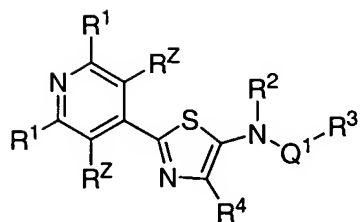
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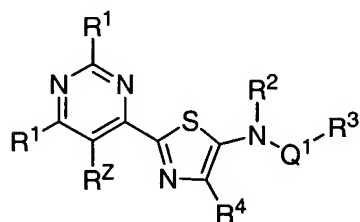
II-E



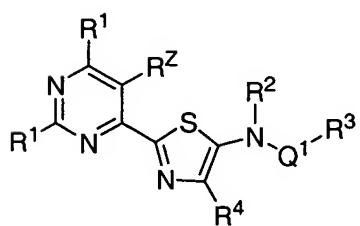
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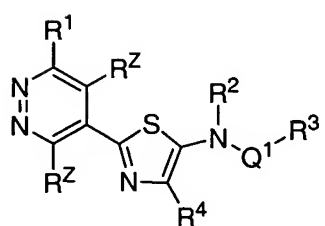
III-A



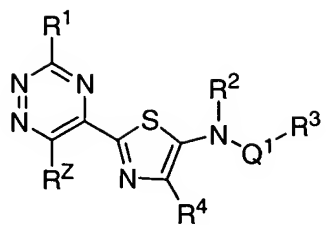
III-B



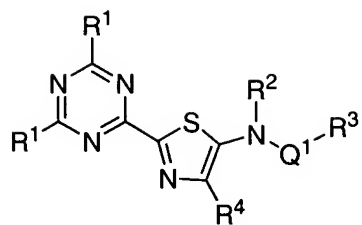
III-C



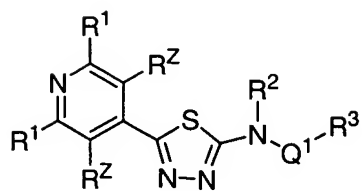
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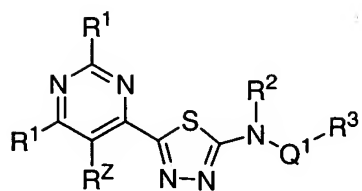
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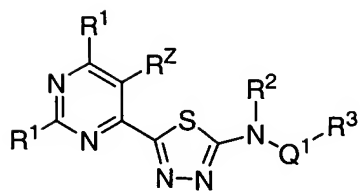
III-F



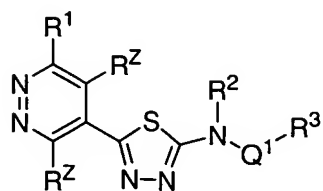
IV-A



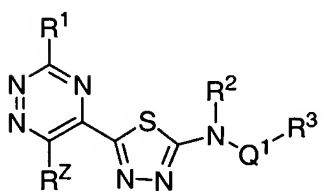
IV-B



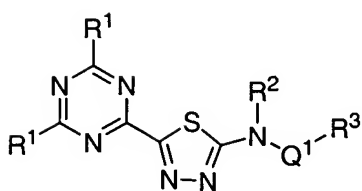
IV-C



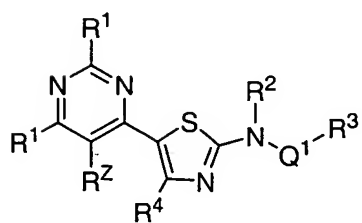
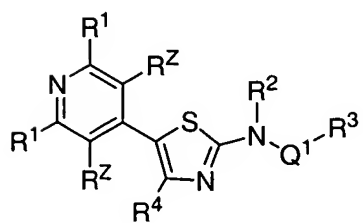
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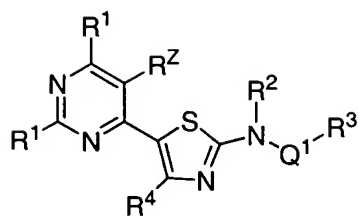
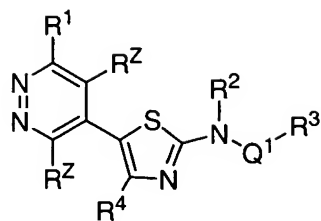
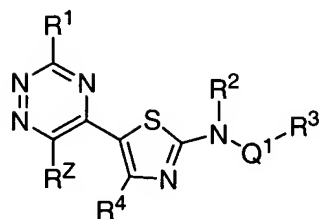
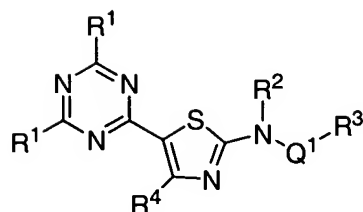
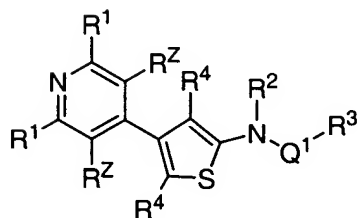
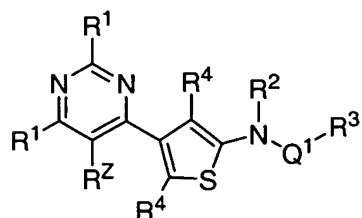
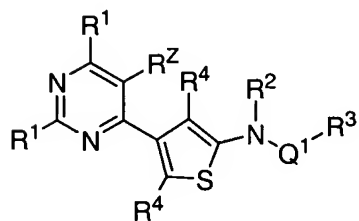
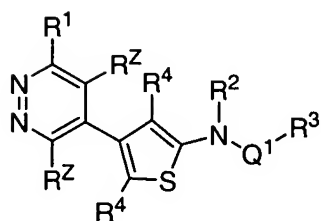


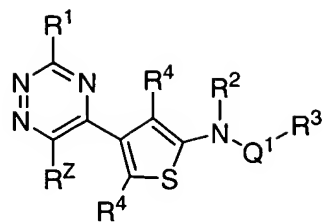
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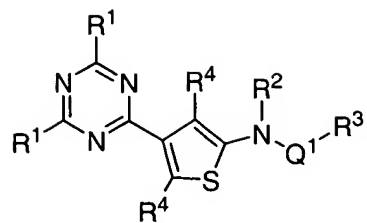
IV-F



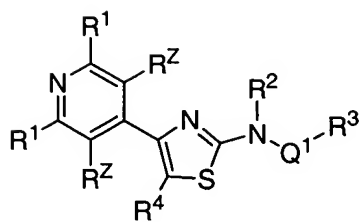
V-A**V-B****V-C****V-D****V-E****V-F****VI-A****VI-B****VI-C****VI-D**



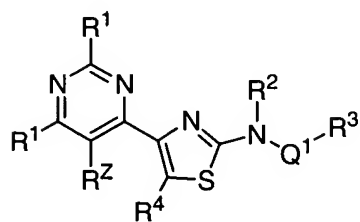
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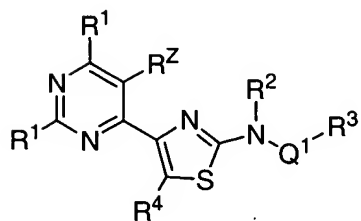
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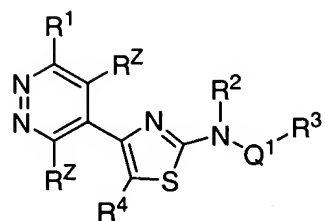
VII-A



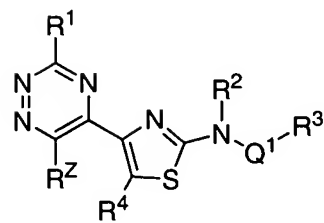
VII-B



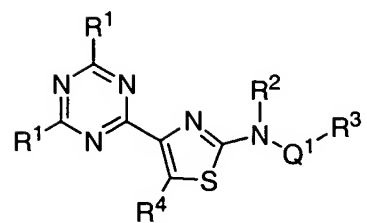
VII-C



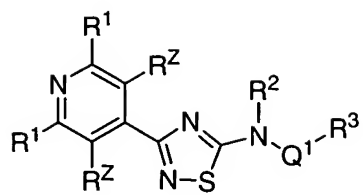
VII-D



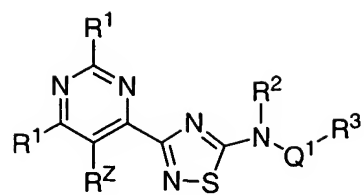
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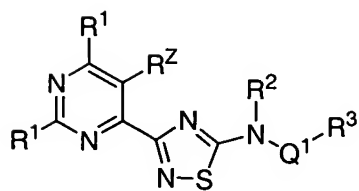
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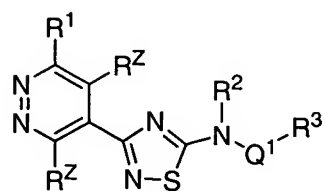
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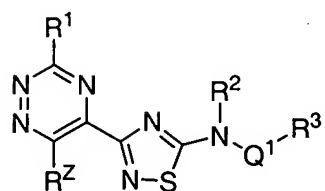
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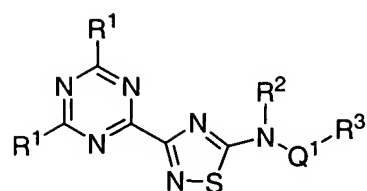
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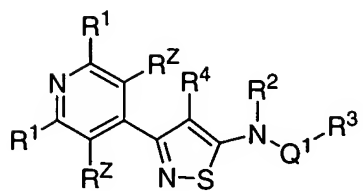
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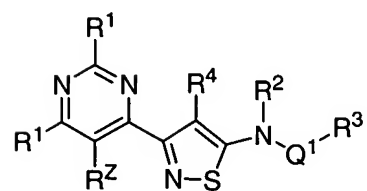
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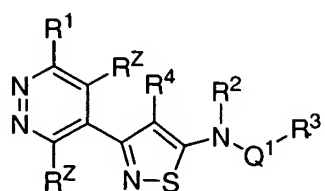
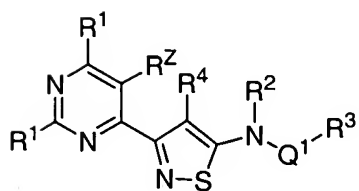
VIII-F



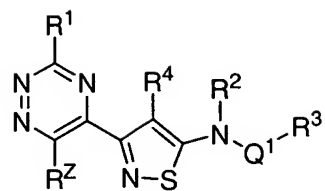
IX-A



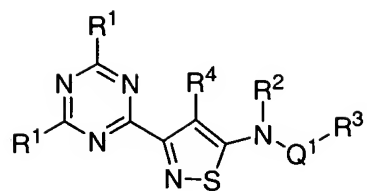
IX-B



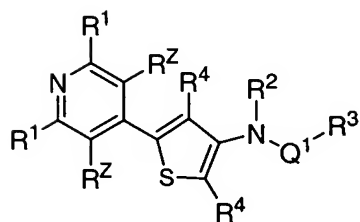
IX-C



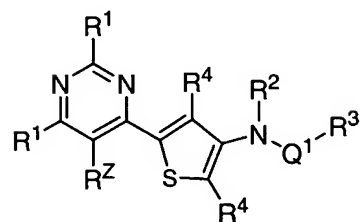
IX-D



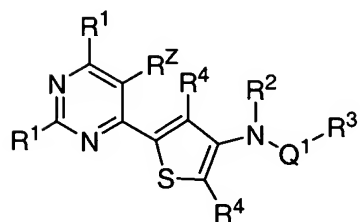
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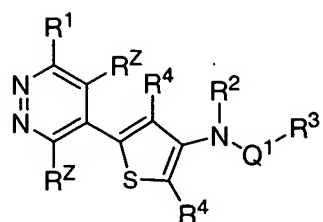
IX-F



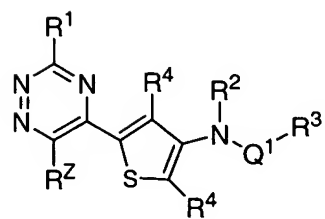
X-A



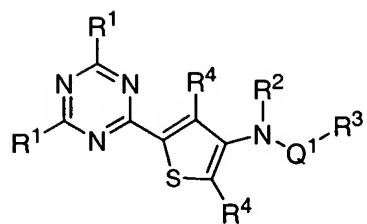
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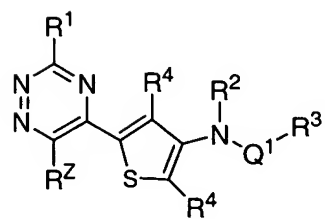
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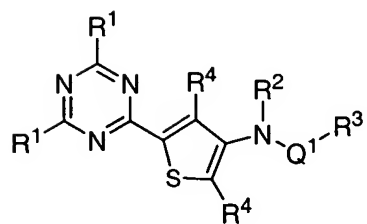
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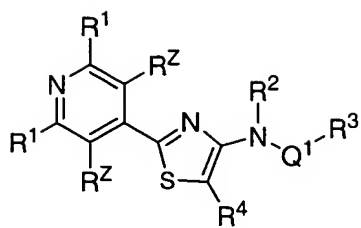


X-E

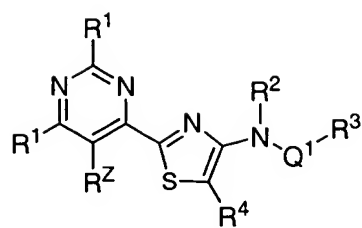


X-F

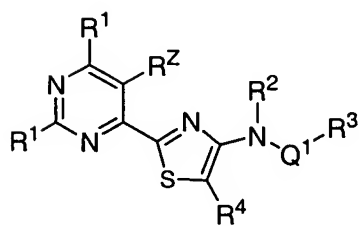




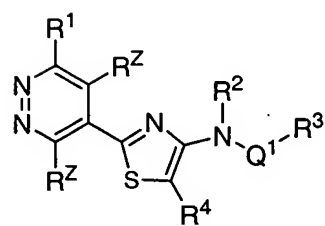
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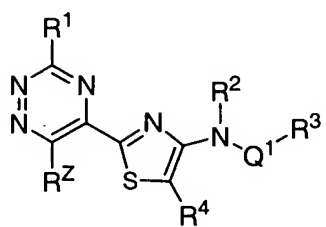
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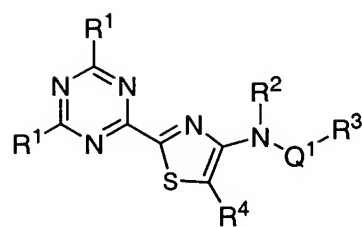
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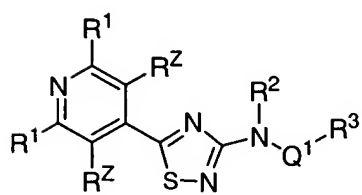
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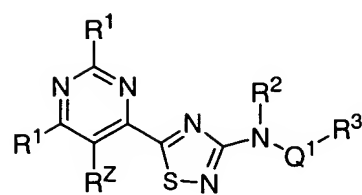
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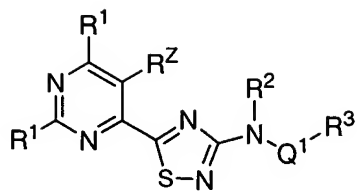
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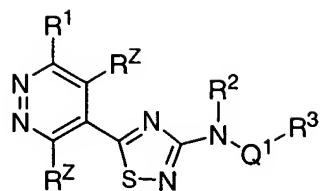
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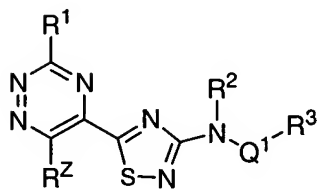
XII-B



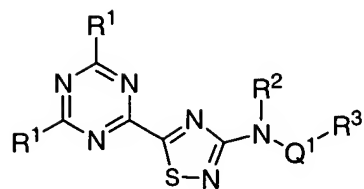
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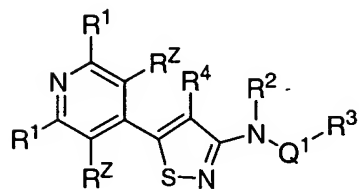
XII-D



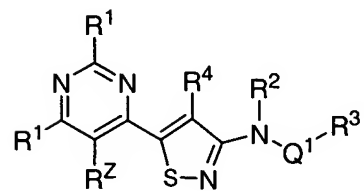
XII-E



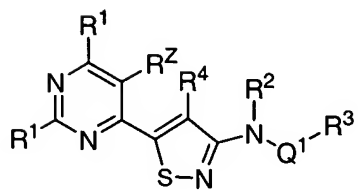
XII-F



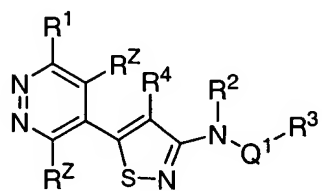
XIII-A



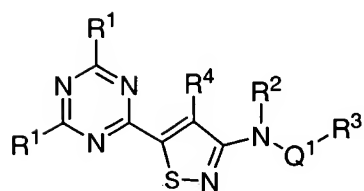
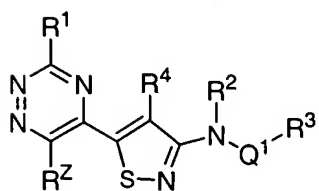
XIII-B



XIII-C



XIII-D



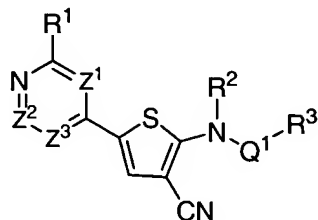
XIII-E

XIII-F

[0073] In general, for compounds of formulas **I**, **I-A-i**, **I-B-i**, **I-C-i**, **I-A-ii**, **I-B-ii**, and **I-C-ii**, (and subsets of formula **II-A**, **II-B**, **II-C**, **II-D**, **II-E**, **II-F**, **III-A**, **III-B**, **III-C**, **III-D**, **III-E**, **III-F**, **IV-A**, **IV-B**, **IV-C**, **IV-D**, **IV-E**, **IV-F**, **V-A**, **V-B**, **V-C**, **V-D**, **V-E**, **V-F**, **VI-A**, **VI-B**, **VI-C**, **VI-D**, **VI-E**, **VI-F**, **VII-A**, **VII-B**, **VII-C**, **VII-D**, **VII-E**, **VII-F**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **IX-A**, **IX-B**, **IX-C**, **IX-D**, **IX-E**, **IX-F**, **X-A**, **X-B**, **X-C**, **X-D**, **X-E**, **X-F**, **XI-A**, **XI-B**, **XI-C**, **XI-D**, **XI-E**, **XI-F**, **XII-A**, **XII-B**, **XII-C**, **XII-D**, **XII-E**, **XII-F**, **XIII-A**, **XIII-B**, **XIII-C**, **XIII-D**, **XIII-E**, and **XIII-F**) each occurrence of R^1 is independently halogen, CN, NO_2 , or V_mR , and each occurrence of R^Z is independently halogen, CN, NO_2 , or U_nR' . In certain embodiments, R^1 groups are hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OH, OR, SR, or $N(R)_2$. In other embodiments R^1 groups are hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $NH(CH_2)_2NHCH_3$, $NH(cyclopropyl)$, $NH(CH_2)cyclopropyl$, or $NH(CH_2)_2N(CH_3)_2$. Exemplary R^Z groups are each independently hydrogen, halogen, C_1 - C_4 aliphatic, OH, OR', or $N(R)(R')$. In certain embodiments, R^Z groups are each independently hydrogen, halogen, Me, OH, OMe, NH_2 , or $N(CH_3)_2$.

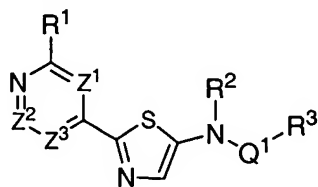
[0074] As described generally above, the thiadiazole, thiazole, thiophene, and isothiazole rings are each optionally substituted with zero, one or two occurrences of R^4 , as valency permits, wherein each occurrence of R^4 is independently halogen, CN, NO_2 , or V_mR . In some embodiments, R^4 groups are each independently hydrogen, C_1 - C_6 aliphatic, $-CN$, $-COR$, $-COOR$, $CON(R)_2$, or halogen.

[0075] In certain embodiments, for thiophene compounds of general formula **II**, one occurrence of R^4 is hydrogen and the other occurrence of R^4 is CN and compounds have the general structure **II-a**:



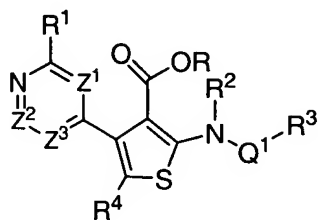
II-a

[0076] In yet other embodiments, for thiazole compounds of general formula **III**, R^4 is hydrogen and compounds have the general structure **III-a**:



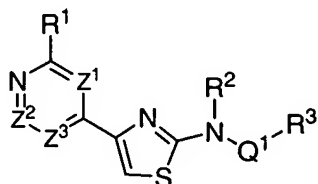
III-a

[0077] In certain embodiments, for thiophene compounds of general formula **VI**, one occurrence of R^4 is hydrogen and the other occurrence of R^4 is -COOR and compounds have the general structure **VI-a**:



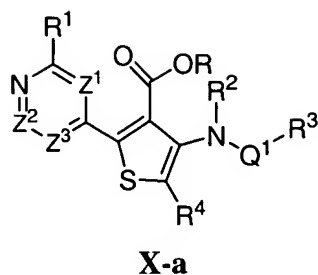
VI-a

[0078] In yet other embodiments, for thiazole compounds of general formula **VII**, R^4 is hydrogen and compounds have the general structure **VII-a**:

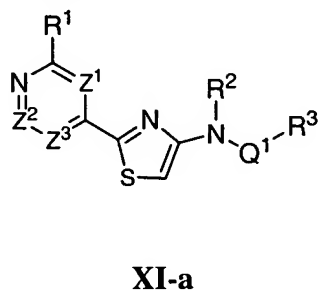


VII-a

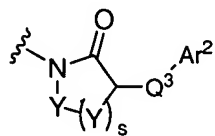
[0079] In certain other embodiments, for thiophene compounds of general formula **X**, one occurrence of R^4 is hydrogen and the other occurrence of R^4 is C(=O)OR and compounds have the general structure **X-a**:



[0080] In yet other preferred embodiments, for thiazole compounds of general formula **XI**, R^4 is hydrogen and compounds have the general structure **XI-a**:

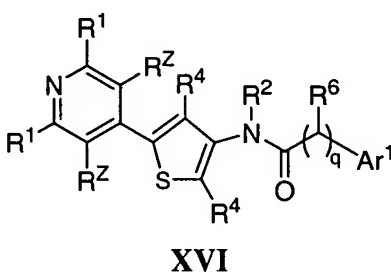
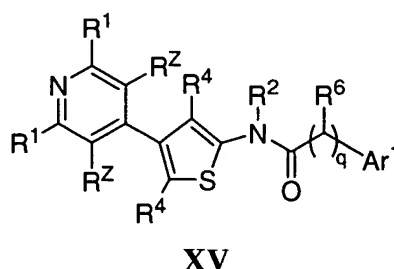
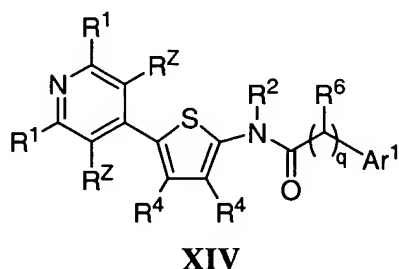


[0081] It will also be appreciated that for each of the above-described compounds **I**, and subsets of formula **II-A**, **II-B**, **II-C**, **II-D**, **II-E**, **II-F**, **III-A**, **III-B**, **III-C**, **III-D**, **III-E**, **III-F**, **IV-A**, **IV-B**, **IV-C**, **IV-D**, **IV-E**, **IV-F**, **V-A**, **V-B**, **V-C**, **V-D**, **V-E**, **V-F**, **VI-A**, **VI-B**, **VI-C**, **VI-D**, **VI-E**, **VI-F**, **VII-A**, **VII-B**, **VII-C**, **VII-D**, **VII-E**, **VII-F**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **IX-A**, **IX-B**, **IX-C**, **IX-D**, **IX-E**, **IX-F**, **X-A**, **X-B**, **X-C**, **X-D**, **X-E**, **X-F**, **XI-A**, **XI-B**, **XI-C**, **XI-D**, **XI-E**, **XI-F**, **XII-A**, **XII-B**, **XII-C**, **XII-D**, **XII-E**, **XII-F**, **XIII-A**, **XIII-B**, **XIII-C**, **XIII-D**, **XIII-E**, **XIII-F**, **II-a**, **III-a**, **VI-a**, **VII-a**, **X-a**, and **XI-a**, in some embodiments R^3 is Q^2-Ar^1 , wherein Q^2 and Ar^1 are described generally and in subsets above and herein. In other exemplary embodiments, for each of the above-described classes and subclasses of compounds, R^2 and Q^1-R^3 , taken together with the nitrogen atom, form the cyclic group:

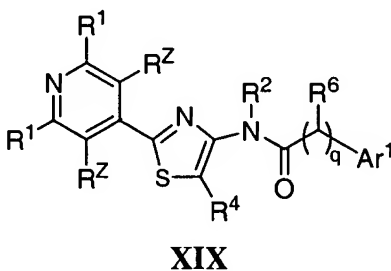
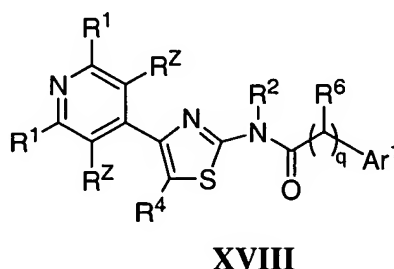
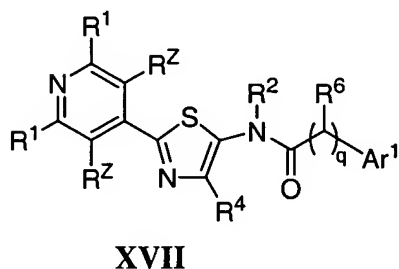


, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, $-CO-$, $-CS-$, $-SO_2-$, $-O-$, $-S-$, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR' , wherein Q^3 , Ar^2 , and R^5 are described generally above and in classes and subclasses above and herein.

[0082] It will be appreciated that for compounds as described above, certain additional compounds are of special interest. For example, in certain exemplary embodiments, thiophene compounds are provided where Q^1 is $-\text{CO}-$, Q^2 is CHR^6 , q is 1, 2, or 3, and compounds have one of formulas **XIV**, **XV**, or **XVI**:



[0083] In other embodiments, thiazole compounds are provided where Q^1 is $-\text{CO}-$, Q^2 is CHR^6 , q is 1, 2 or 3, and compounds have one of formulas **XVII**, **XVIII**, or **XIX**:



[0084] In certain embodiments, for compounds of formulas **XIV**, **XV**, **XVI**, **XVII**, **XVIII**, or **XIX**, compound variables are selected from one of more of the following groups:

a) each occurrence of R^1 is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OR, SR, or $N(R)_2$;

b) each occurrence of R^1 is independently hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $NH(CH_2)_2NHCH_3$, $NH(cyclopropyl)$, $NH(CH_2)cyclopropyl$, or $NH(CH_2)_2N(CH_3)_2$;

c) each occurrence of R^Z is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OH, $O(R')$, or $N(R)(R')$;

d) each occurrence of R^Z is independently hydrogen, halogen, Me, OH, OMe, NH_2 , or $N(Me)_2$;

e) R^2 is hydrogen, or is U_nR' , where n is 1, and U is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NR-$, $-CH_2CH_2O-$, $-CH_2CH_2S-$, $-CH_2CH_2NR-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2NR-$, $-CH_2CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2CH_2NR-$, $-CH_2CH_2OCH_2CH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_3NHCH_2CH_2-$, or $-CH_2CH_2NHCH_2CH_2-$, and R' groups are hydrogen, C_1 - C_4 alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R' , taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered heterocyclyl ring;

f) each occurrence of R^4 is independently hydrogen, C_{1-6} aliphatic, CN, COR, COOR, $CON(R)_2$, or halogen;

g) q is 1, 2, or 3;

h) R^6 is R' , $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-OR'$, $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring;

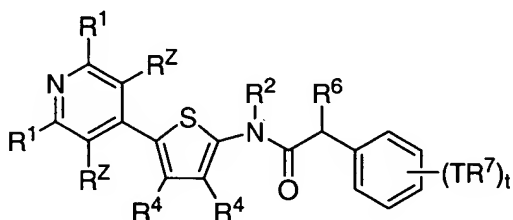
i) R^6 is CH_2OH , CH_2CH_2OH , OH, OMe, OEt, NH_2 , $NH(Me)$, $NH(Et)$, $N(Me)(Me)$, CH_2NH_2 , $CH_2CH_2NH_2$, $NHCO_2t$ -butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NH(Et)$, $NHCH_2pyridyl$, $NHSO_2phenyl$, $NHC(O)CH_2C(O)Ot$ -butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$ -imidazol-4-yl;

j) Ar^1 is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units

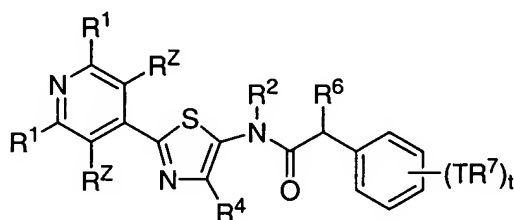
are optionally and independently replaced by $-O-$, $-NR-$, $-S-$, $-SO_2-$, $-COO-$, $-CO-$, $-OSO_2-$, $-NRSO_2$, $-CONR-$, or $-SO_2NR-$, and R^7 is R' or halogen; or

k) Ar^1 is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}alkyl$, $-OR'$, $-SR'$, $-CF_3$, $-OCF_3$, $-SCF_3$, $-F$, $-Cl$, I , $-Br$, $-COOR'$, $-COR'$, $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-C(O)N(R)(R')$, $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, $-N(R)(R')$, $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, $CON(R)(R')$, or $-OSO_2R'$.

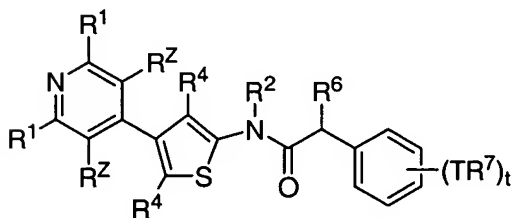
[0085] In other embodiments, for the thiophene and thiazole compounds of formulas **XIV** through **XIX**, q is 1, and Ar^1 is optionally substituted phenyl and compounds of general formula **XIV-A** through **XIX-A** are provided:



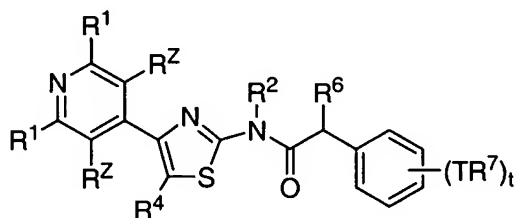
XIV-A



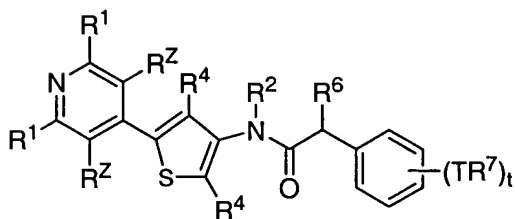
XV-A



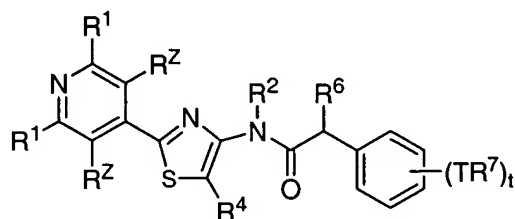
XVI-A



XVII-A



XVIII-A



XIX-A

wherein R^1 , R^Z , R^2 , R^4 , R^6 , T , R^7 and t are as defined generally and in classes and subclasses above and herein.

[0086] In preferred embodiments, for compounds of formula **XIV-A** through **XIX-A**:

each occurrence of R^1 is hydrogen;

each occurrence of R^Z is hydrogen;

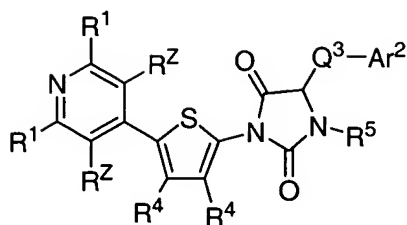
R^2 is hydrogen, or is U_nR' , where n is 1, and U is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NR-$, $-CH_2CH_2O-$, $-CH_2CH_2S-$, $-CH_2CH_2NR-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2NR-$, $-CH_2CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2CH_2NR-$, $-CH_2CH_2OCH_2CH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_3NHCH_2CH_2-$, or $-CH_2CH_2NHCH_2CH_2-$, and R' groups are hydrogen, C_1 - C_4 alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R' , taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered heterocyclyl ring;

each occurrence of R^4 is independently hydrogen, C_{1-6} aliphatic, CN, COR, COOR, $CON(R)_2$, or halogen;

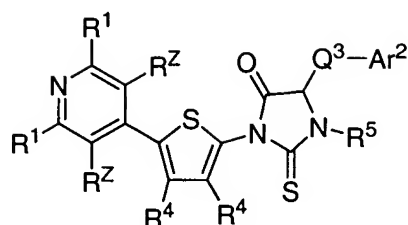
R^6 is R' , $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-OR'$, $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$; and

t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}$ alkyl, $-OR'$, $-SR'$, $-CF_3$, $-OCF_3$, $-SCF_3$, $-F$, $-Cl$, I , $-Br$, $-COOR'$, $-COR'$, $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, $-C(O)N(R)(R')$, $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, $-N(R)(R')$, $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, $CON(R)(R')$, or $-OSO_2R'$.

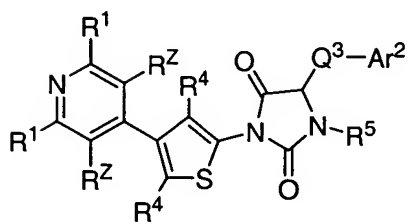
[0087] Other subsets include those compounds where R^2 and Q^1 - R^3 , taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have the general formula **XX** through **XXV**:



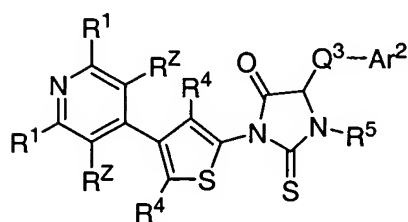
XX



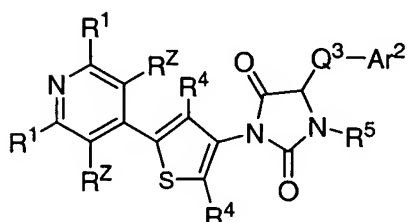
XXI



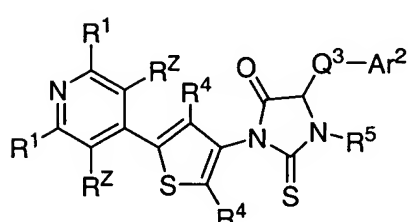
XXII



XXIII

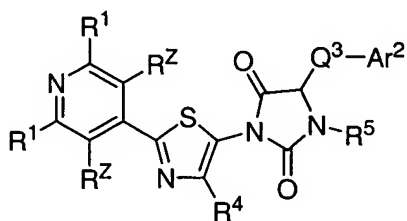


XXIV

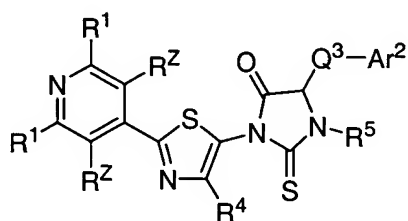


XXV

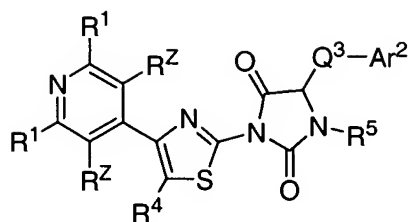
[0088] In other embodiments, thiazole compounds are provided where R^2 and Q^1-R^3 , taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have the general formula **XXVI** through **XXXI**:



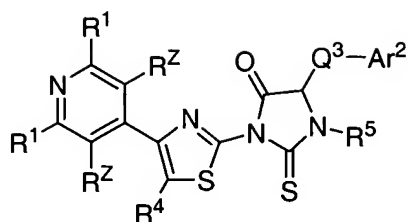
XXVI



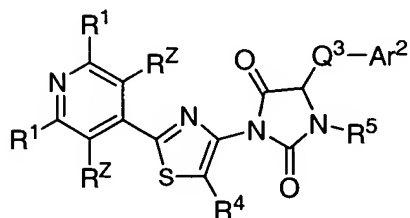
XXVII



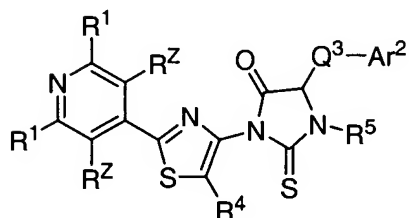
XXVIII



XXIX

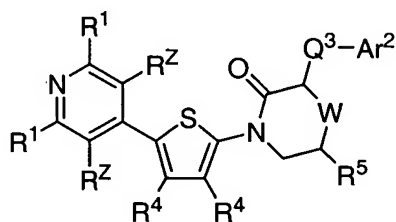


XXX

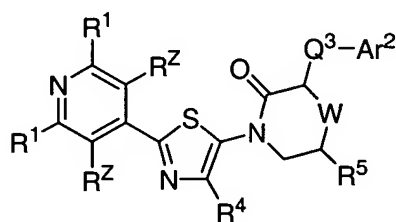


XXXI

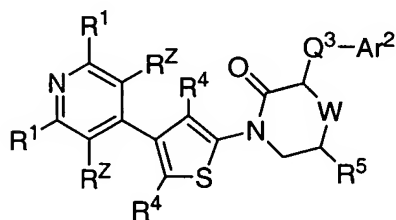
[0089] In still other embodiments, thiophene and thiazole compounds are provided where R^2 and Q^1-R^3 , taken together with the atoms to which they are bound form a 6-membered cyclic group, and compounds have the general formula **XXXII** through **XXXVII**:



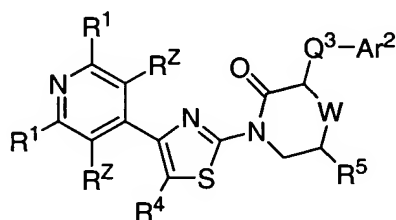
XXXII



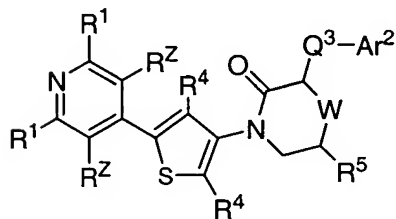
XXXIII



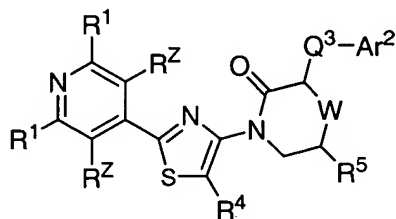
XXXIV



XXXV



XXXVI



XXXVII

wherein W is O, NR⁵, or CHR⁵.

[0090] In certain embodiments, for compounds of formulas **XX** through **XXXVII** compound variables are selected from one of more of the following groups:

a) each occurrence of R¹ is hydrogen, halogen, optionally substituted C₁-C₄aliphatic, OR, SR, or N(R)₂;

b) each occurrence of R^Z is independently hydrogen, halogen, optionally substituted C₁-C₄aliphatic, OH, OR' or N(R)(R');

c) each occurrence of R⁴ is independently hydrogen, C₁₋₆aliphatic, CN, COR, COOR, CON(R)₂, or halogen;

d) R⁵ is hydrogen, (CH₂)₃OR', (CH₂)₂OR', (CH₂)OR', (CH₂)₃N(R')₂, (CH₂)₂N(R')₂, (CH₂)N(R')₂, or C₁₋₄aliphatic;

e) Q³ is a direct bond, or is -(CHR⁶)_q-, -(CHR⁶)_qO-, -(CHR⁶)_qS-, -(CHR⁶)_qS(O)₂-, -(CHR⁶)_qS(O)-, -(CHR⁶)_qNR-, or -(CHR⁶)_qC(O)-, wherein q is 0, 1, 2, or 3; and

f) Ar² is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **n**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C₁₋₆ alkylidene chain wherein one or two methylene units are optionally and independently replaced by -O-, -NR-, -S-, -SO₂-, -COO-, -CO-, -OSO₂-, -NRSO₂-, -CONR-, or -SO₂NR-, and R⁷ is R' or halogen.

[0091] In certain other embodiments, for compounds of formulas **XX** through **XXXVII** compound variables are selected from one of more of the following groups:

a) each occurrence of R¹ is independently hydrogen, halogen, -CH₃, -CH₂CH₃, -OH, -OCH₃, -SCH₃, -NH₂, -N(CH₃)₂, -N(CH₂CH₃)₂, NH(CH₂)₂NHCH₃, NH(cyclopropyl), NH(CH₂)cyclopropyl, or NH(CH₂)₂N(CH₃)₂;

b) each occurrence of R^Z is independently hydrogen, halogen, Me, OH, OMe, NH₂, or N(Me)₂;

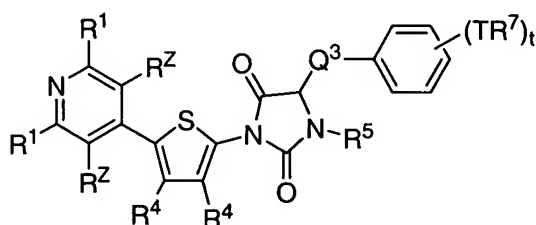
c) each occurrence of R⁴ is independently hydrogen, C₁₋₆aliphatic, CN, COR, COOR, CON(R)₂, or halogen;

d) R⁵ is hydrogen, (CH₂)₃OR', (CH₂)₂OR', (CH₂)OR', (CH₂)₃N(R')₂, (CH₂)₂N(R')₂, (CH₂)N(R')₂, or C₁₋₄aliphatic;

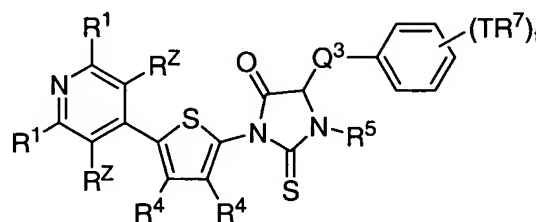
e) Q^3 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3; and

f) Ar^2 is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **n**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}alkyl$, $-OR'$, $-SR'$, $-CF_3$, $-OCF_3$, $-SCF_3$, $-F$, $-Cl$, I , $-Br$, $-COOR'$, $-COR'$, $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, $-C(O)N(R)(R')$, $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, $-N(R)(R')$, $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, $CON(R)(R')$, or $-OSO_2R'$.

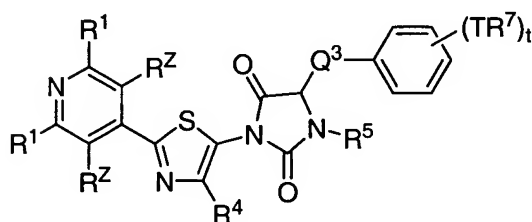
[0092] In other embodiments, for the thiophene and thiazole compounds of formulas as described above, Ar^2 is optionally substituted phenyl and compounds of general formula **XX-A**, through **XXXVII** are provided:



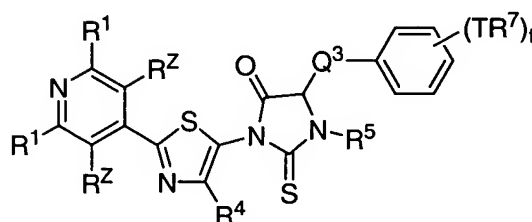
XX-A



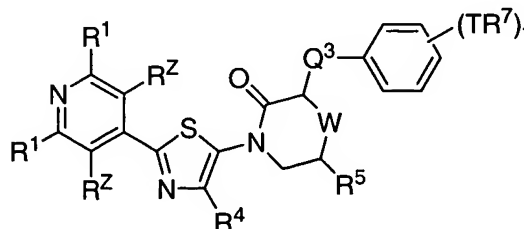
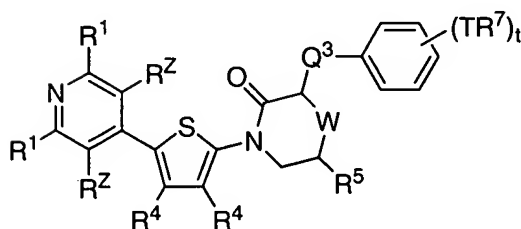
XXI-A

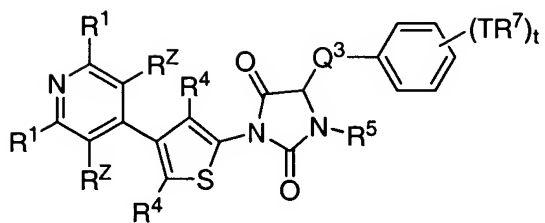
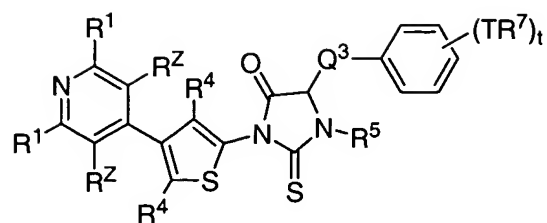
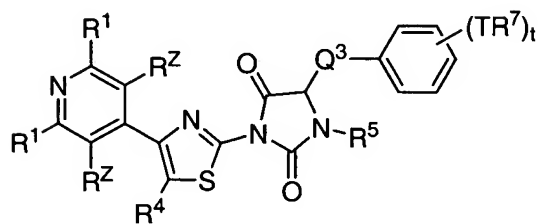
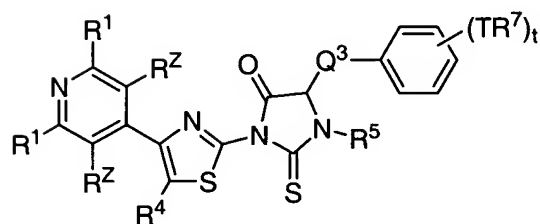
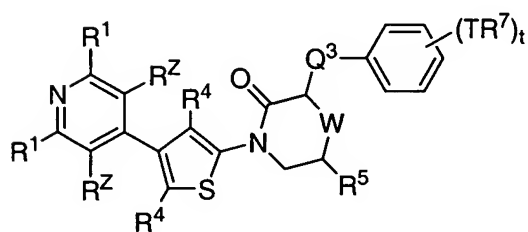
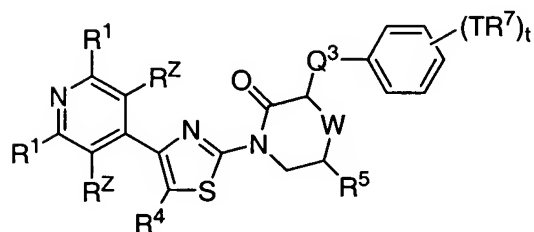
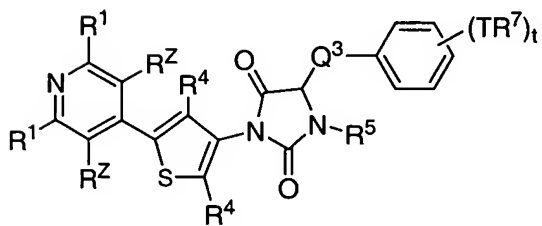
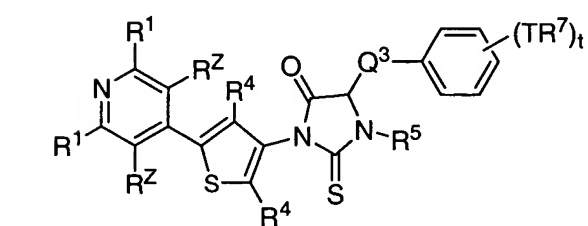


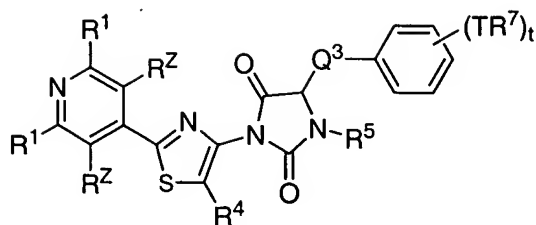
XXII-A



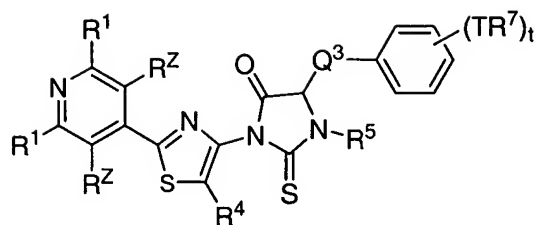
XXIII-A



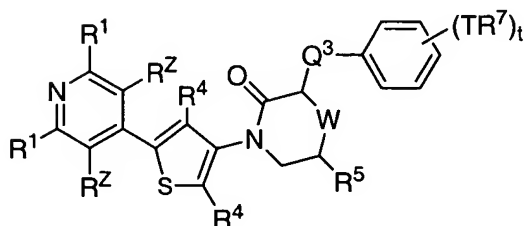
XXIV-A**XXV-A****XXVI-A****XXVII-A****XXVIII-A****XXIX-A****XXX-A****XXXI-A****XXXII-A****XXXIII-A**



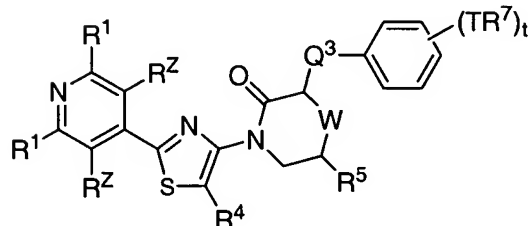
XXXIV-A



XXXV-A



XXXVI-A



XXXVII-A

wherein R^1 , R^Z , R^4 , R^5 , Q^3 , T , R^7 , t , and W are as defined generally and in classes and subclasses above and herein.

[0093] In preferred embodiments, for compounds of formula **XX-A** through **XXXVII-A**:

each occurrence of R^1 is hydrogen;

each occurrence of R^Z is hydrogen;

each occurrence of R^4 is independently hydrogen, C_{1-6} aliphatic, CN, COR, COOR, CON(R)₂, or halogen;

R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic;

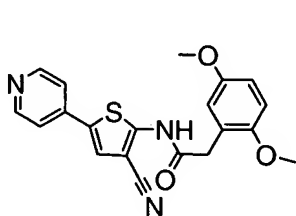
Q^3 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3; and

t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}$ alkyl, $-OR'$, $-SR'$, $-CF_3$, $-OCF_3$, $-SCF_3$, $-F$, $-Cl$, I , $-Br$, $-COOR'$, $-COR'$, $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, $-C(O)N(R)(R')$, $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, $-N(R)(R')$, $-(CH_2)_4N(R)(R')$, $-$

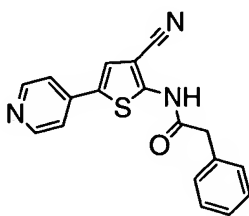
$(\text{CH}_2)_3\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)_2\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)\text{N}(\text{R})(\text{R}')$, or $\text{SO}_2\text{N}(\text{R})(\text{R}')$, $\text{NRSO}_2\text{R}'$, $\text{CON}(\text{R})(\text{R}')$, or $-\text{OSO}_2\text{R}'$.

[0094] Representative examples of compounds of formula **I-A** are set forth below in Table 1 below.

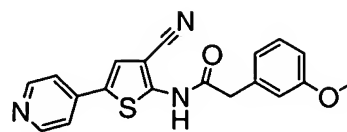
[0095] Table 1. Examples of Compounds of Formula **I-A**:



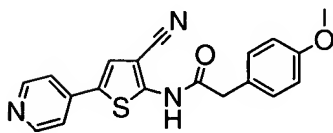
I-A-1



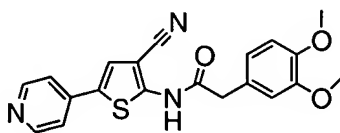
I-A-2



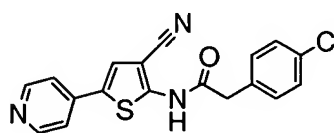
I-A-3



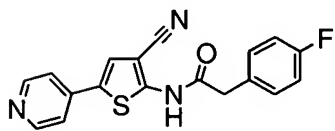
I-A-4



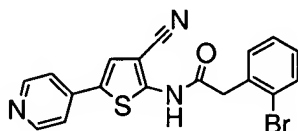
I-A-5



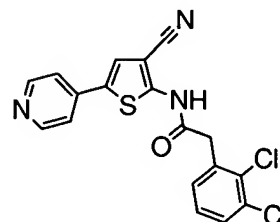
I-A-6



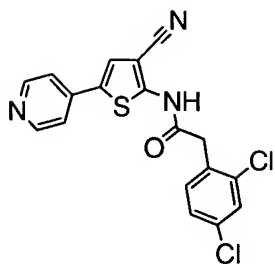
I-A-7



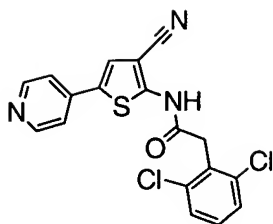
I-A-8



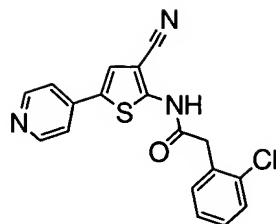
I-A-9



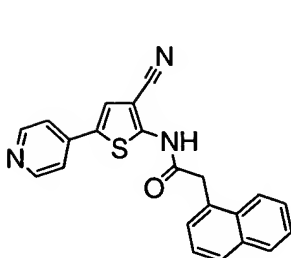
I-A-10



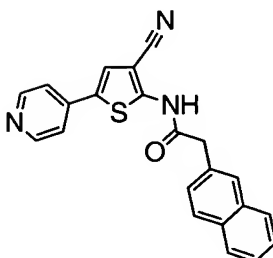
I-A-11



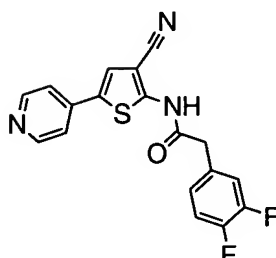
I-A-12



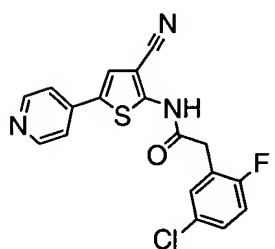
I-A-13



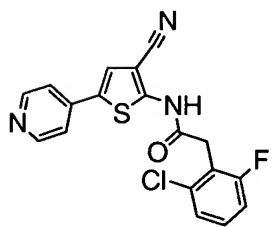
I-A-14



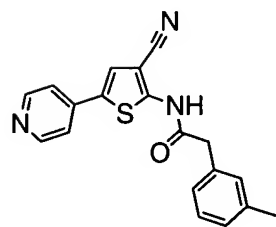
I-A-15



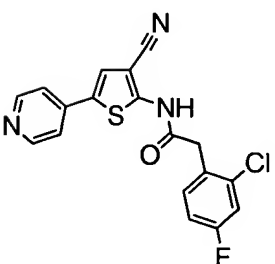
I-A-16



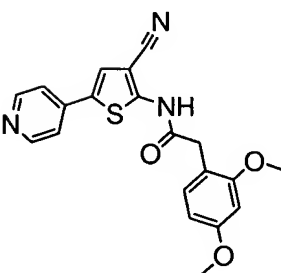
I-A-17



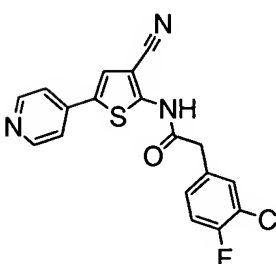
I-A-18



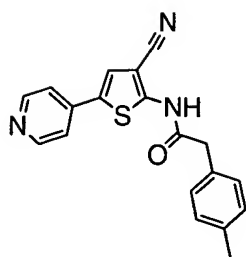
I-A-19



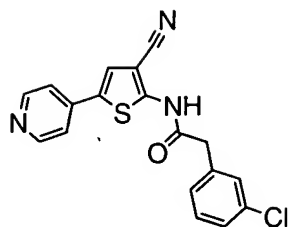
I-A-20



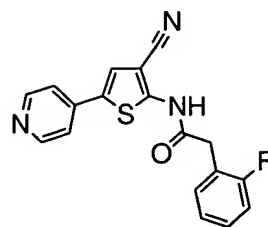
I-A-21



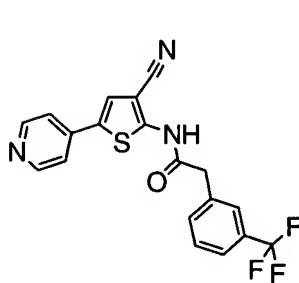
I-A-22



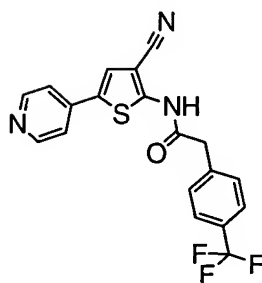
I-A-23



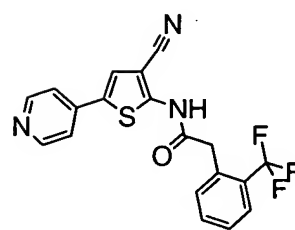
I-A-24



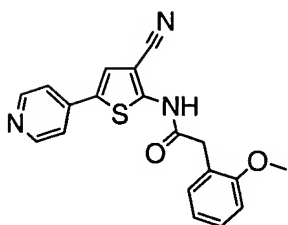
I-A-25



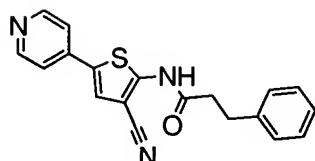
I-A-26



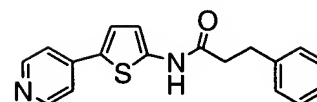
I-A-27



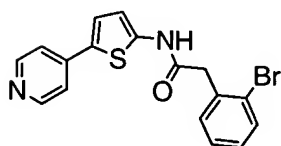
I-A-28



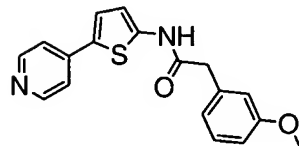
I-A-29



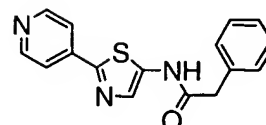
I-A-30



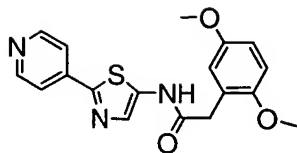
I-A-31



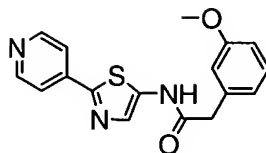
I-A-32



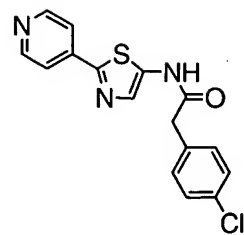
I-A-33



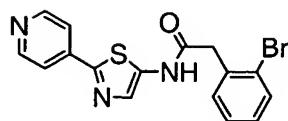
I-A-34



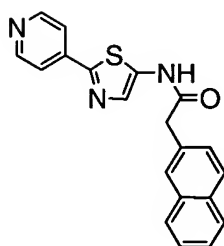
I-A-35



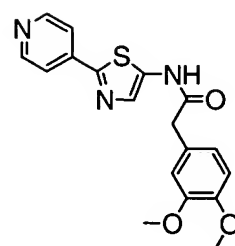
I-A-36



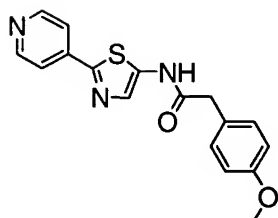
I-A-37



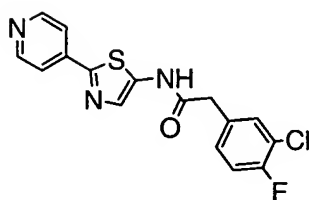
I-A-38



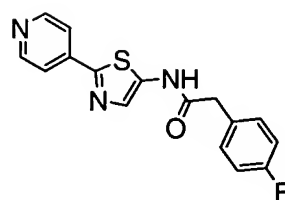
I-A-39



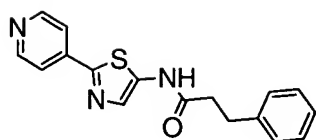
I-A-40



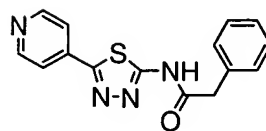
I-A-41



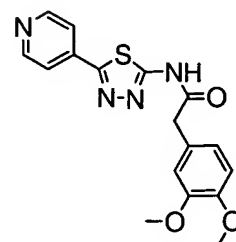
I-A-42



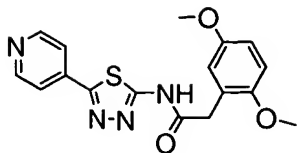
I-A-43



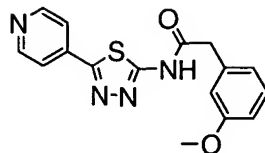
I-A-44



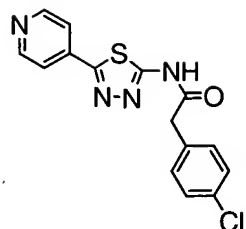
I-A-45



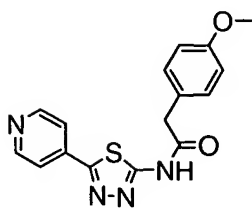
I-A-46



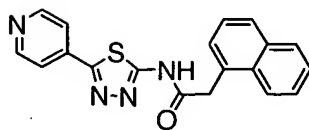
I-A-47



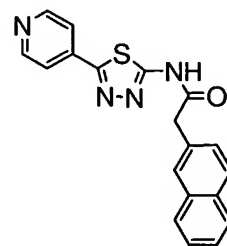
I-A-48



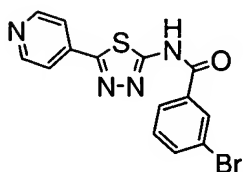
I-A-49



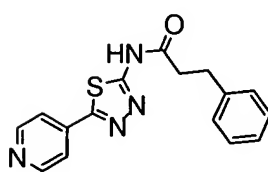
I-A-50



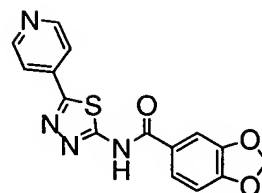
I-A-51



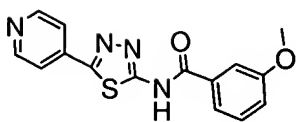
I-A-52



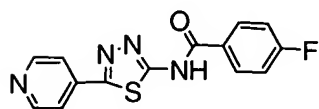
I-A-53



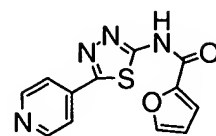
I-A-54



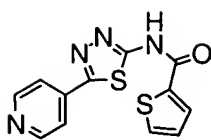
I-A-55



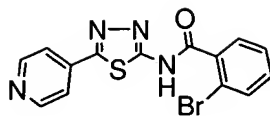
I-A-56



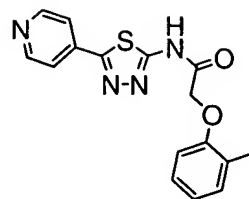
I-A-57



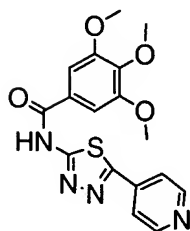
I-A-58



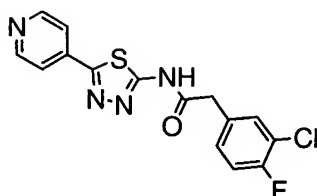
I-A-59



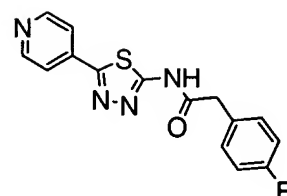
I-A-60



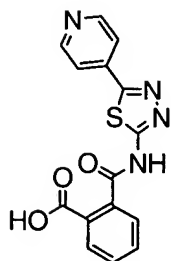
I-A-61



I-A-62



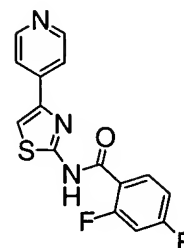
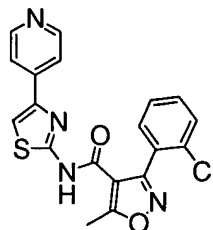
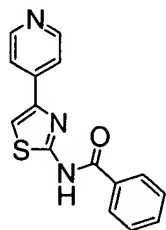
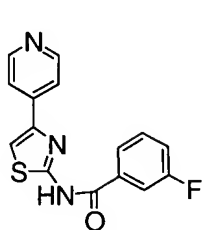
I-A-63

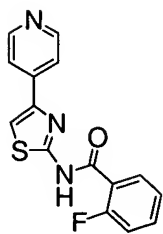
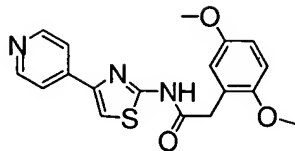
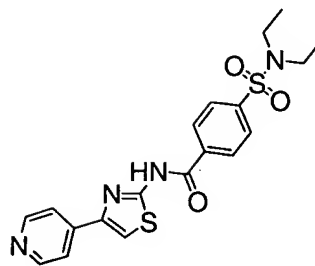
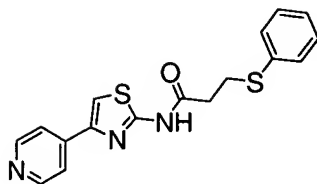
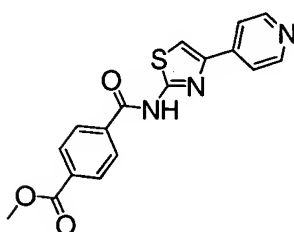
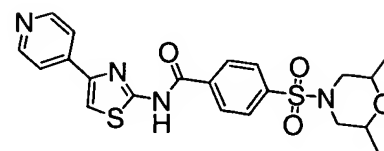
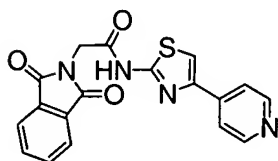
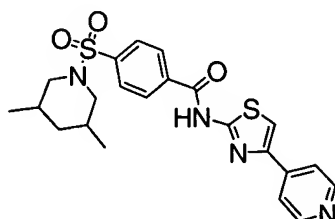
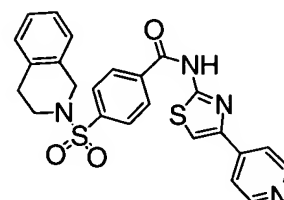
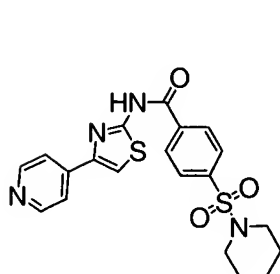
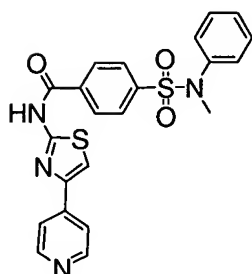
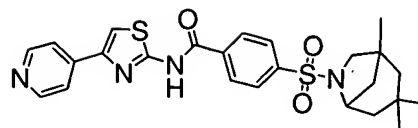


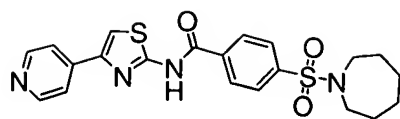
I-A-64

[0096] Representative examples of compounds of formula **I-B** are set forth below in Table 2 below.

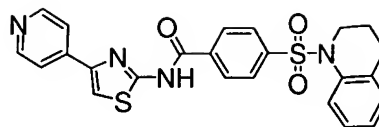
[0097] Table 2. Examples of Compounds of Formula **I-B**:



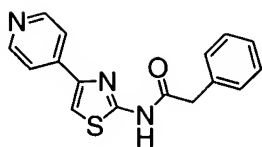
I-B-1**I-B-5****I-B-2****I-B-6****I-B-3****I-B-4****I-B-7****I-B-8****I-B-9****I-B-10****I-B-11****I-B-12****I-B-13****I-B-14****I-B-15****I-B-16**



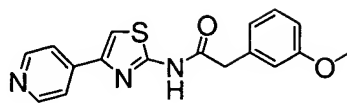
I-B-17



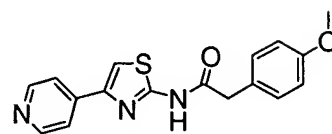
I-B-18



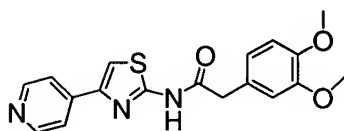
I-B-19



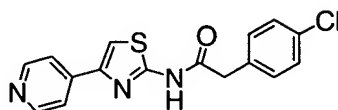
I-B-20



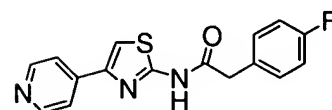
I-B-21



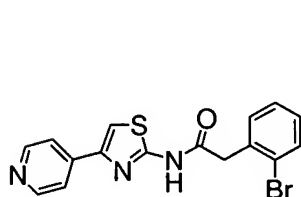
I-B-22



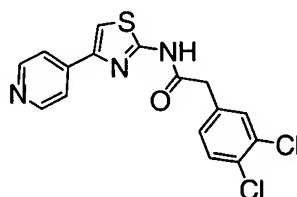
I-B-23



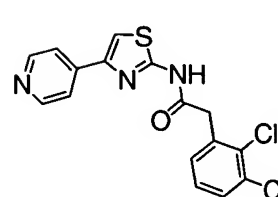
I-B-24



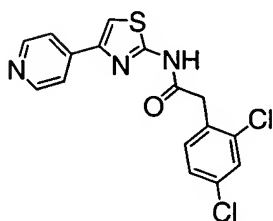
I-B-25



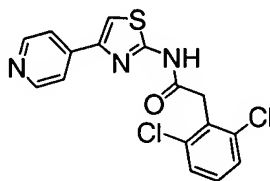
I-B-26



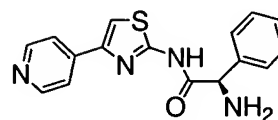
I-B-27



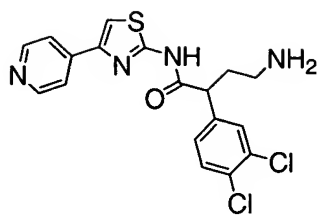
I-B-28



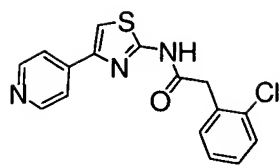
I-B-29



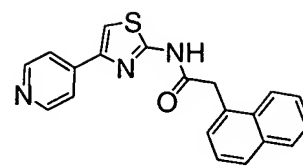
I-B-30



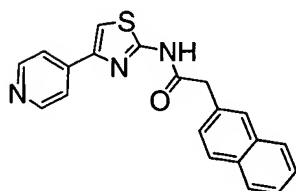
I-B-31



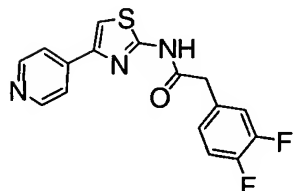
I-B-32



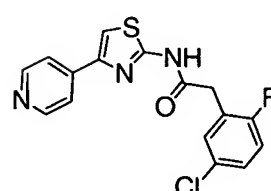
I-B-33



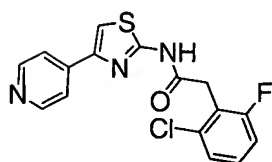
I-B-34



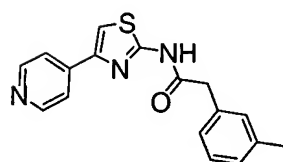
I-B-35



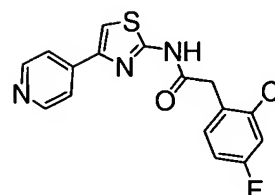
I-B-36



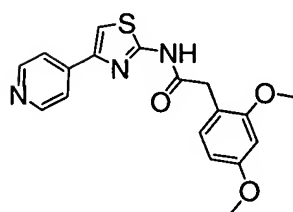
I-B-37



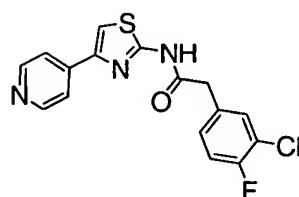
I-B-38



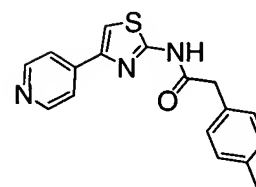
I-B-39



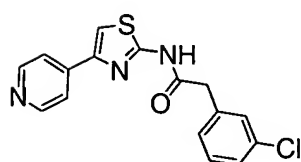
I-B-40



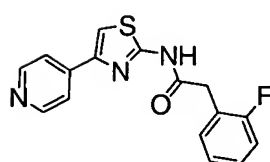
I-B-41



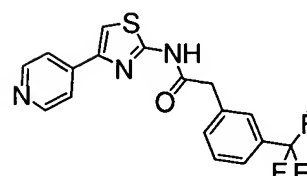
I-B-42



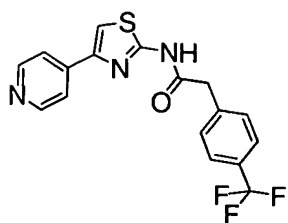
I-B-43



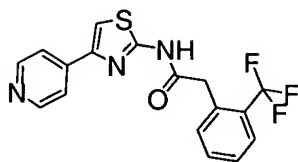
I-B-44



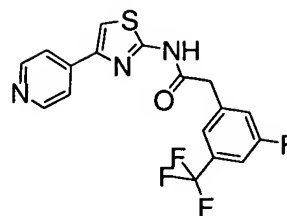
I-B-45



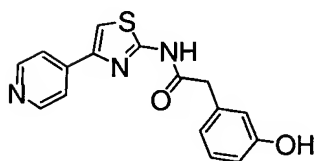
I-B-46



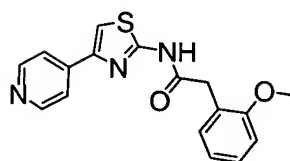
I-B-47



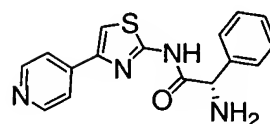
I-B-48



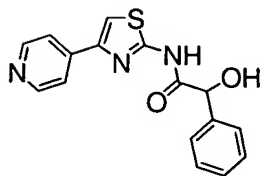
I-B-49



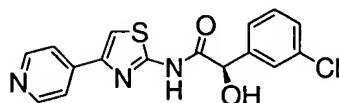
I-B-50



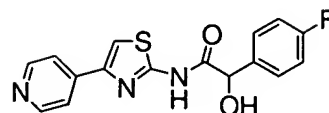
I-B-51



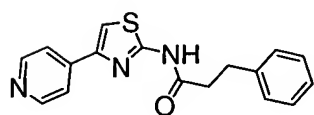
I-B-52



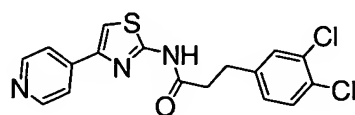
I-B-53



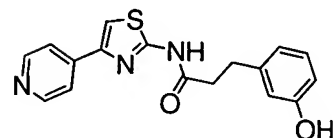
I-B-54



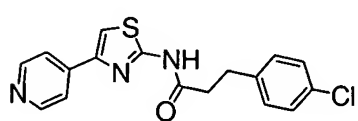
I-B-55



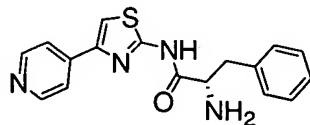
I-B-56



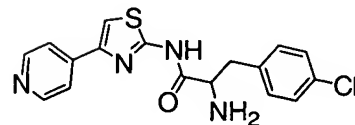
I-B-57



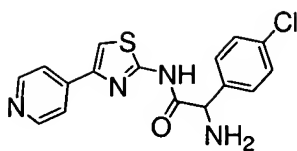
I-B-58



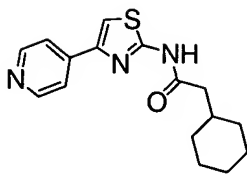
I-B-59



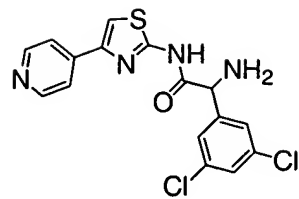
I-B-60



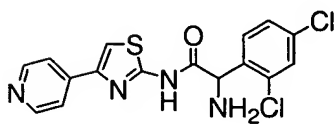
I-B-61



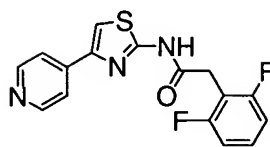
I-B-62



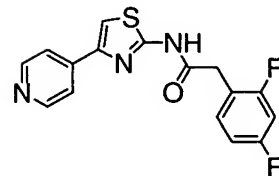
I-B-63



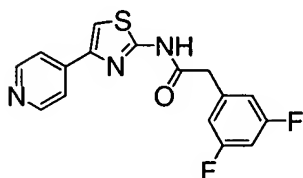
I-B-64



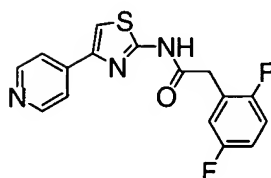
I-B-65



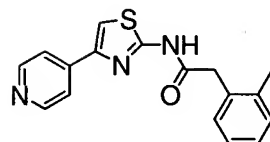
I-B-66



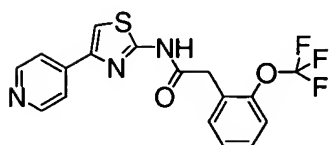
I-B-67



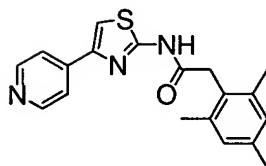
I-B-68



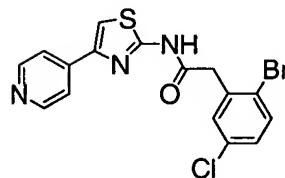
I-B-69



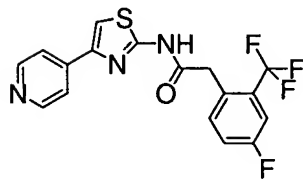
I-B-70



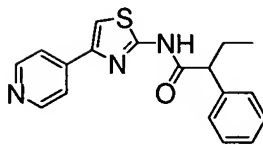
I-B-71



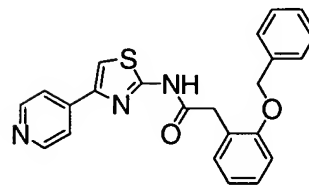
I-B-72



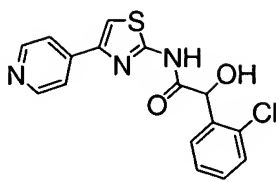
I-B-73



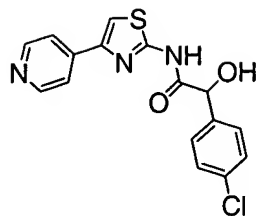
I-B-74



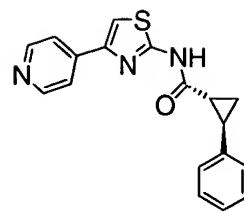
I-B-75



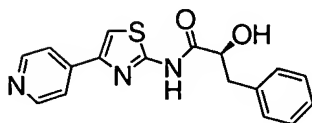
I-B-76



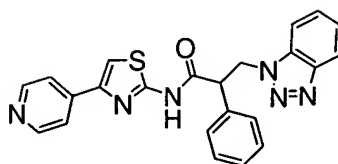
I-B-77



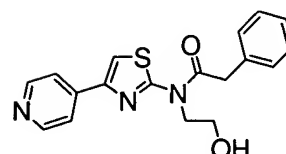
I-B-78



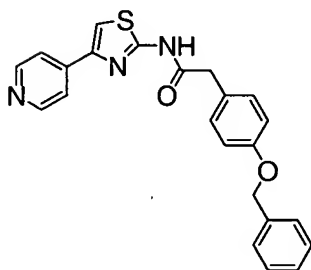
I-B-79



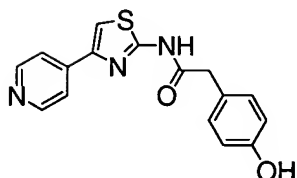
I-B-80



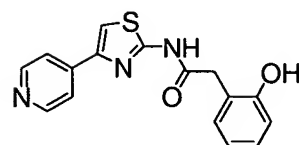
I-B-81



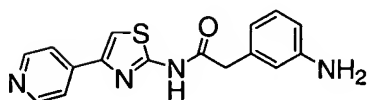
I-B-82



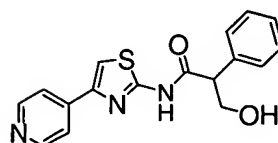
I-B-83



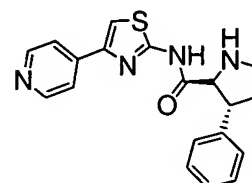
I-B-84



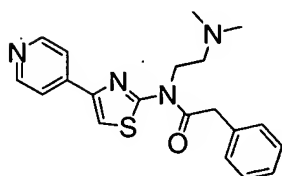
I-B-85



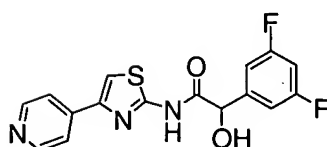
I-B-86



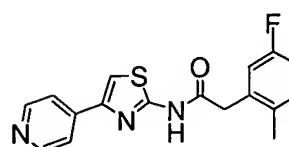
I-B-87



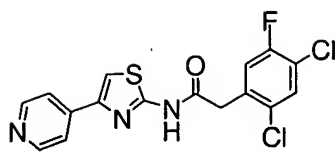
I-B-88



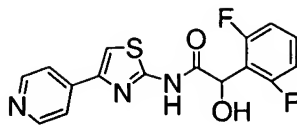
I-B-89



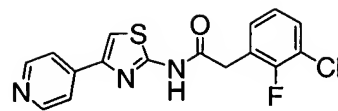
I-B-90



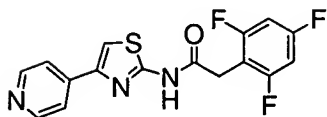
I-B-91



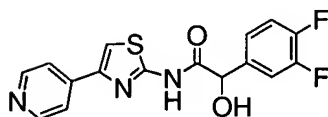
I-B-92



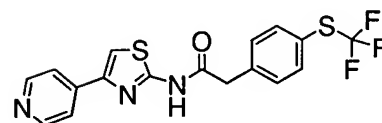
I-B-93



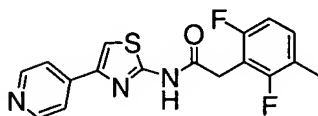
I-B-94



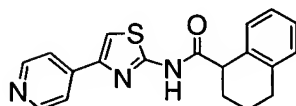
I-B-95



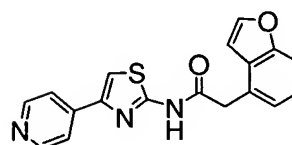
I-B-96



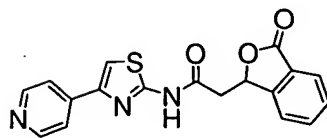
I-B-97



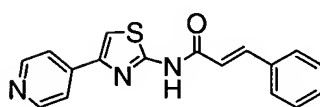
I-B-98



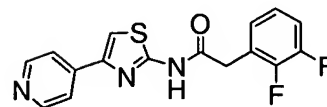
I-B-99



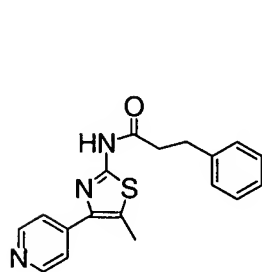
I-B-100



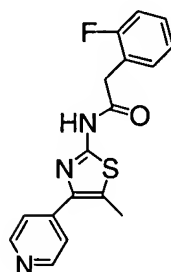
I-B-101



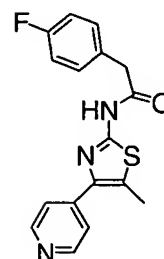
I-B-102



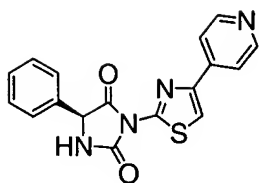
I-B-103



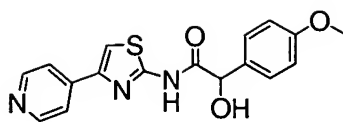
I-B-104



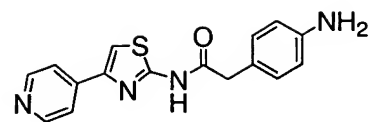
I-B-105



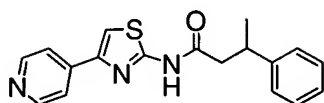
I-B-106



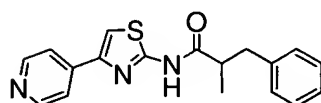
I-B-107



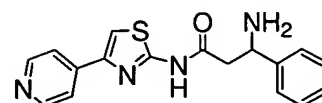
I-B-108



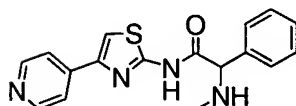
I-B-109



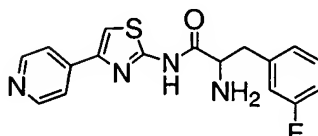
I-B-110



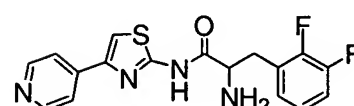
I-B-111



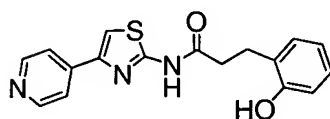
I-B-112



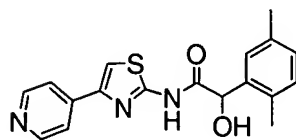
I-B-113



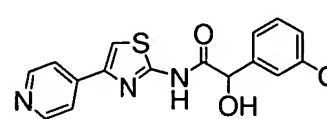
I-B-114



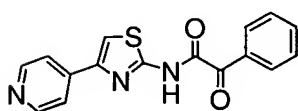
I-B-115



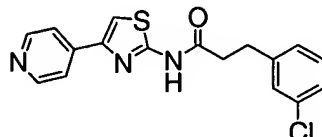
I-B-116



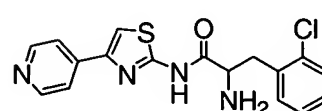
I-B-117



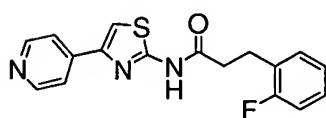
I-B-118



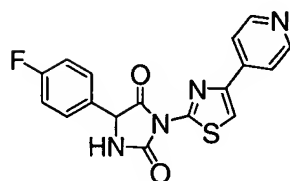
I-B-119



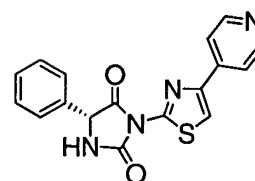
I-B-120



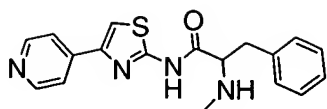
I-B-121



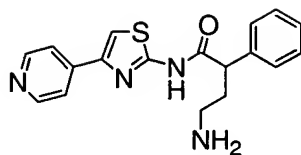
I-B-122



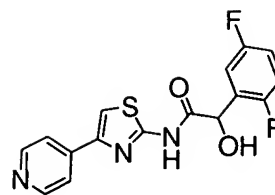
I-B-123



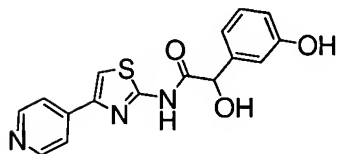
I-B-124



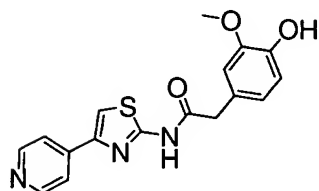
I-B-125



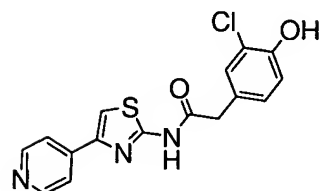
I-B-126



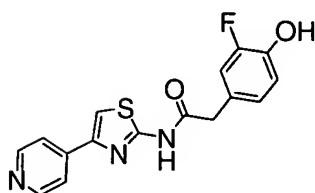
I-B-127



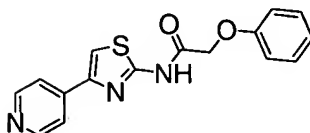
I-B-128



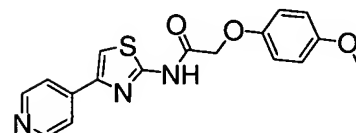
I-B-129



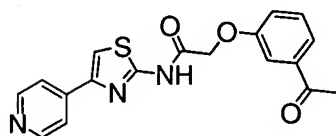
I-B-130



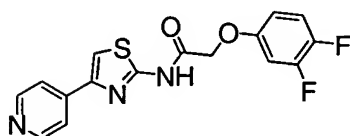
I-B-131



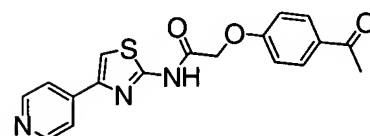
I-B-132



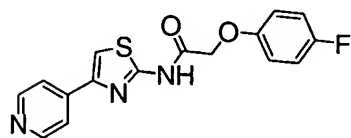
I-B-133



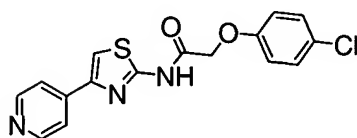
I-B-134



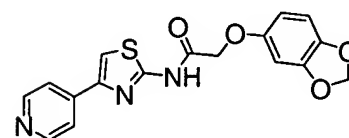
I-B-135



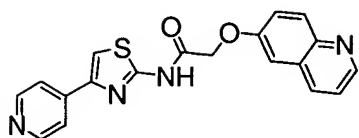
I-B-136



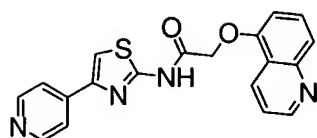
I-B-137



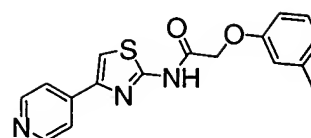
I-B-138



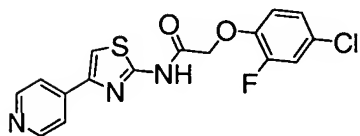
I-B-139



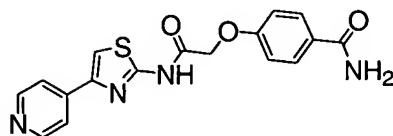
I-B-40



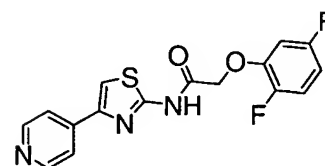
I-B-141



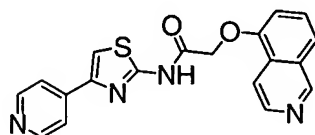
I-B-142



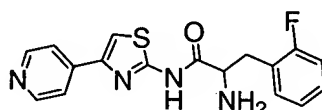
I-B-143



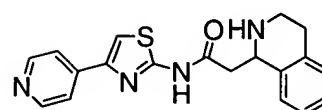
I-B-144



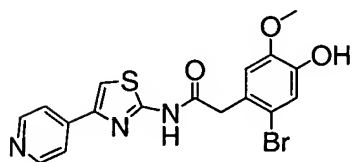
I-B-145



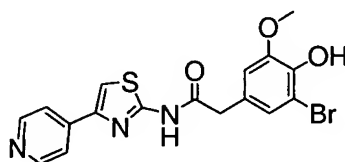
I-B-146



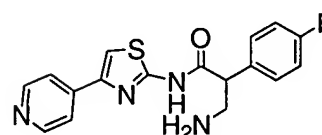
I-B-147



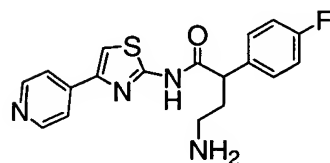
I-B-148



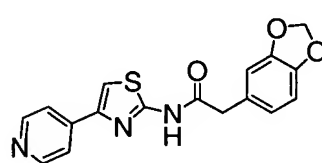
I-B-149



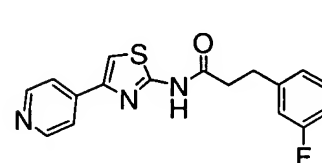
I-B-150



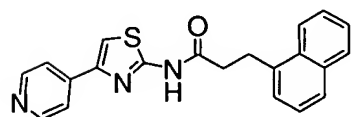
I-B-151



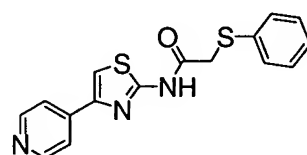
I-B-152



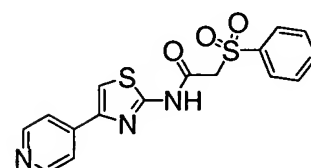
I-B-153



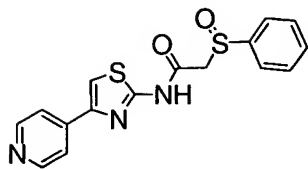
I-B-154



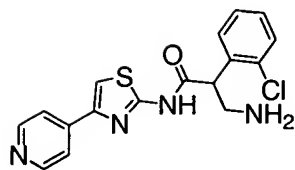
I-B-155



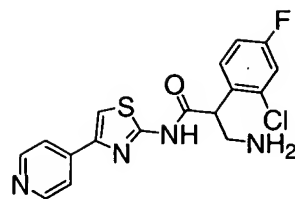
I-B-156



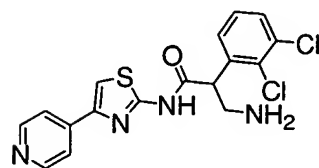
I-B-157



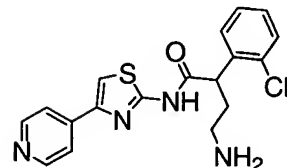
I-B-158



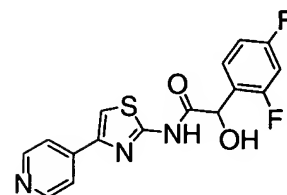
I-B-159



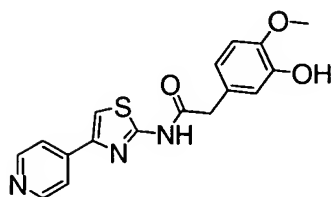
I-B-160



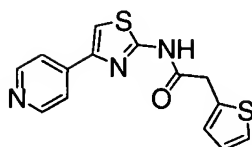
I-B-161



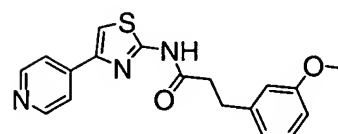
I-B-162



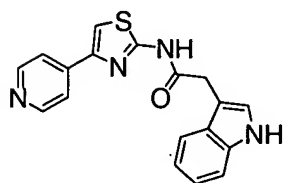
I-B-163



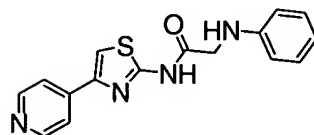
I-B-164



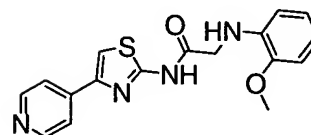
I-B-165



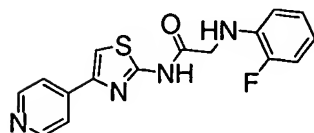
I-B-166



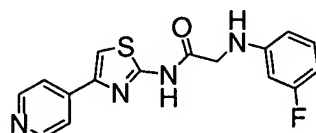
I-B-167



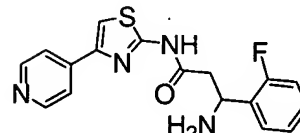
I-B-168



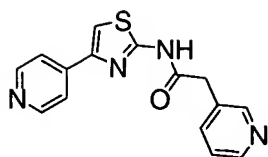
I-B-169



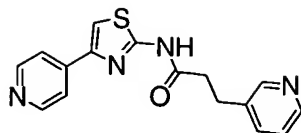
I-B-170



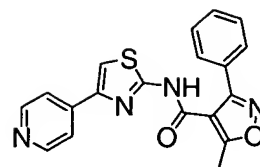
I-B-171



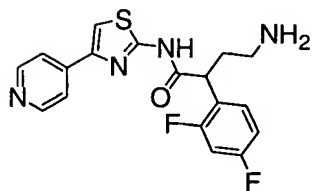
I-B-172



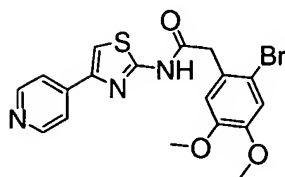
I-B-173



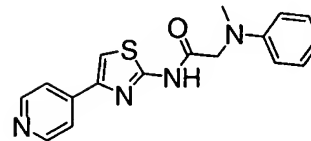
I-B-174



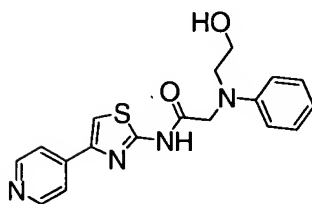
I-B-175



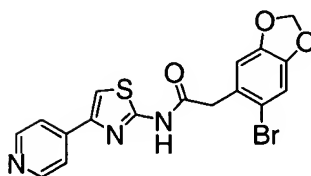
I-B-176



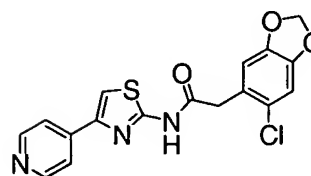
I-B-177



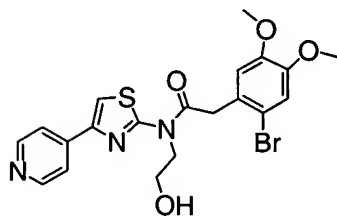
I-B-178



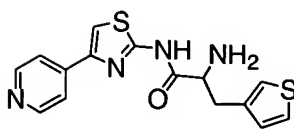
I-B-179



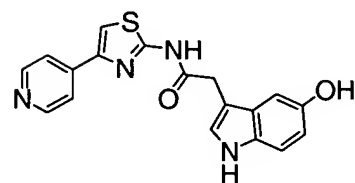
I-B-180



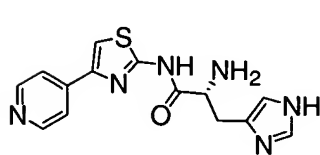
I-B-181



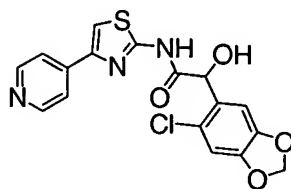
I-B-182



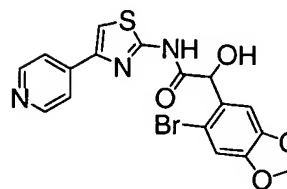
I-B-183



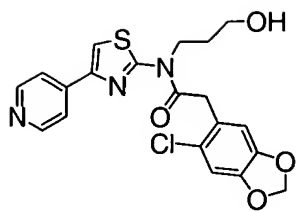
I-B-184



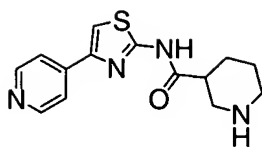
I-B-185



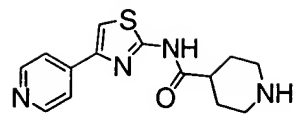
I-B-186



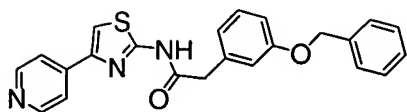
I-B-187



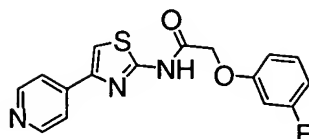
I-B-188



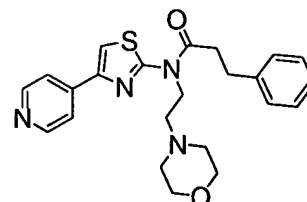
I-B-189



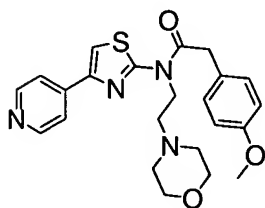
I-B-190



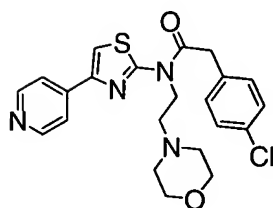
I-B-191



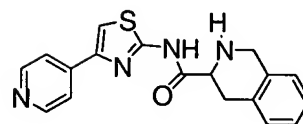
I-B-192



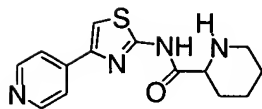
I-B-193



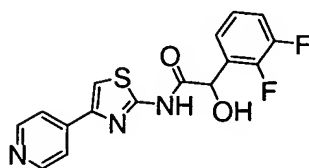
I-B-194



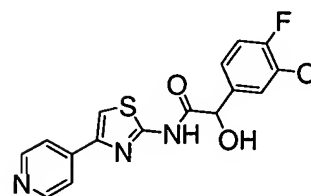
I-B-195



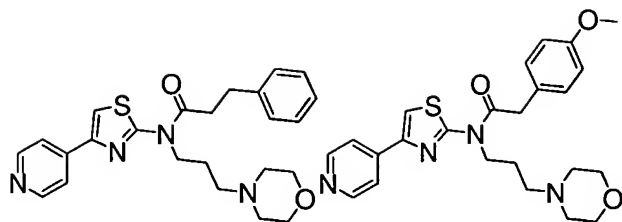
I-B-196



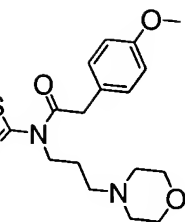
I-B-197



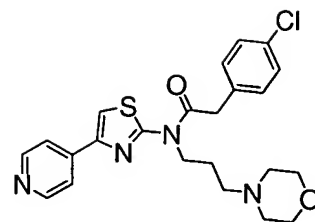
I-B-198



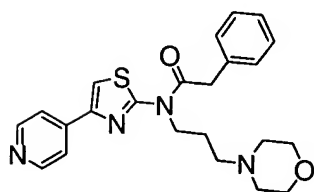
I-B-199



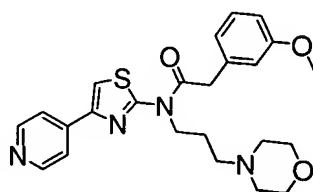
I-B-200



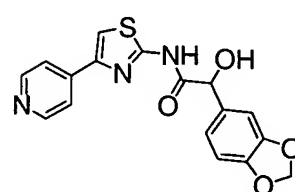
I-B-201



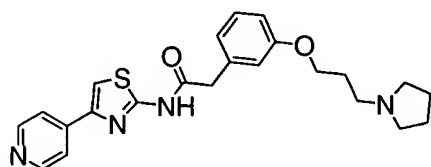
I-B-202



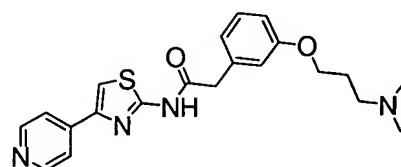
I-B-203



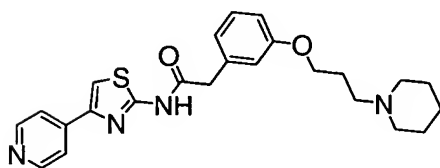
I-B-204



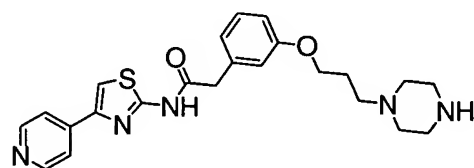
I-B-205



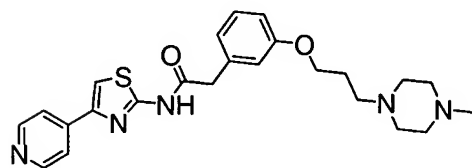
I-B-206



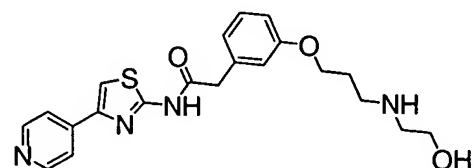
I-B-207



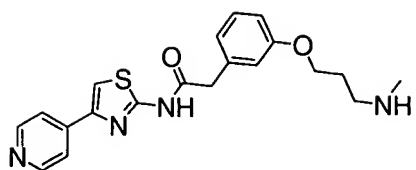
I-B-208



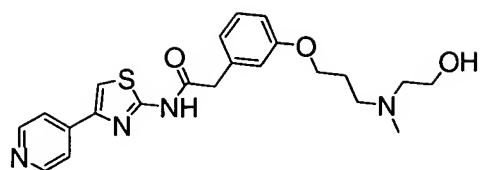
I-B-209



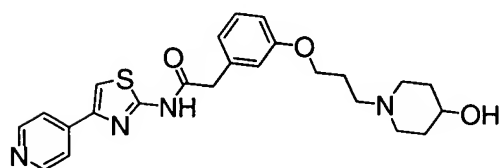
I-B-210



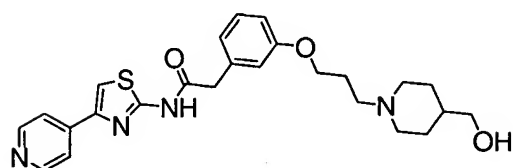
I-B-211



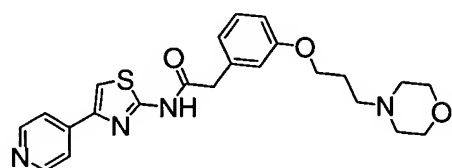
I-B-212



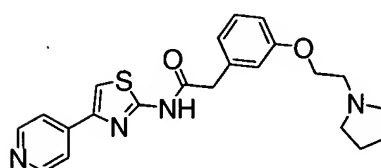
I-B-213



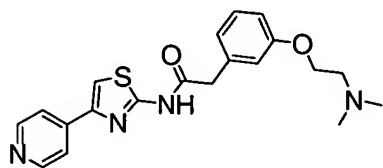
I-B-214



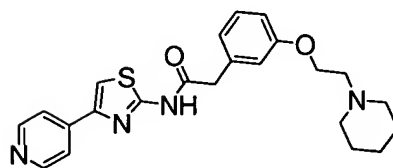
I-B-215



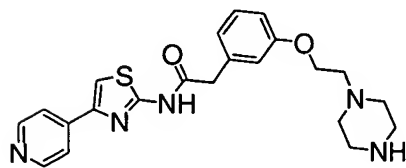
I-B-216



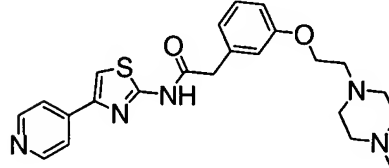
I-B-217



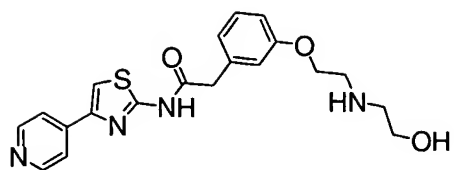
I-B-218



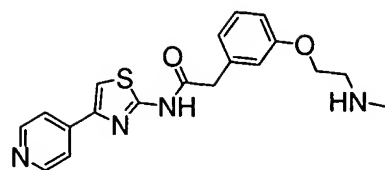
I-B-219



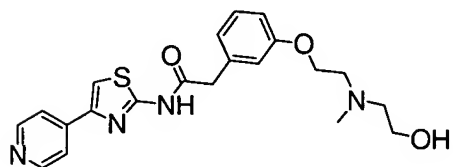
I-B-220



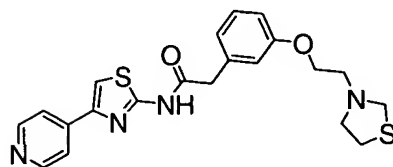
I-B-221



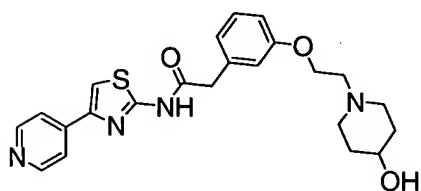
I-B-222



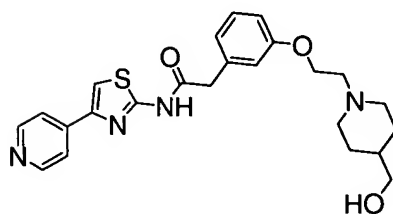
I-B-223



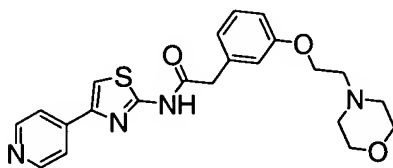
I-B-224



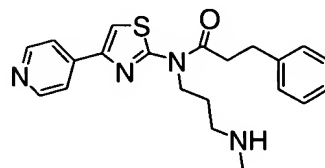
I-B-225



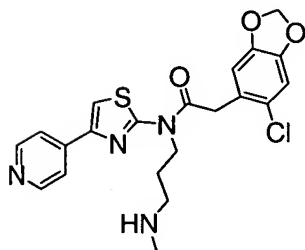
I-B-226



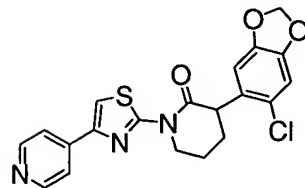
I-B-227



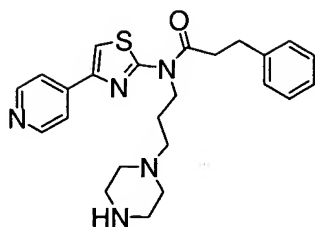
I-B-228



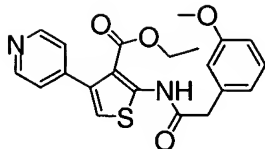
I-B-229



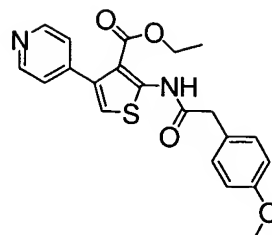
I-B-230



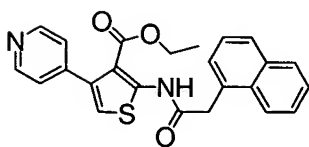
I-B-231



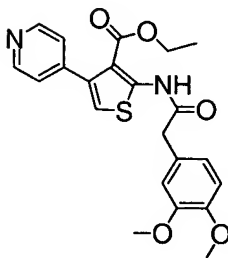
I-B-232



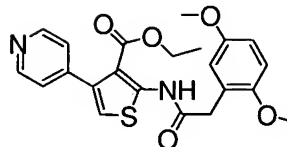
I-B-233



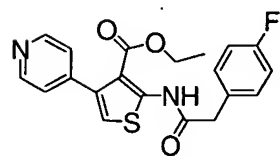
I-B-234



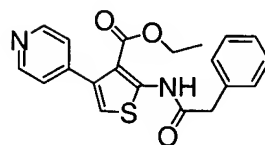
I-B-235



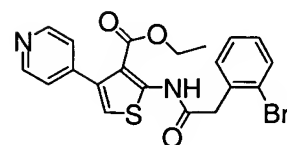
I-B-236



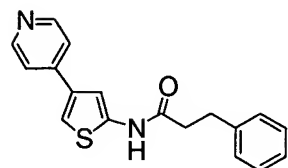
I-B-237



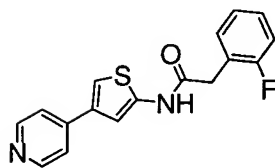
I-B-238



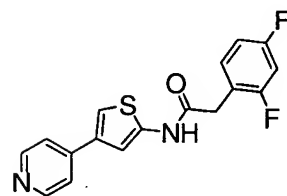
I-B-239



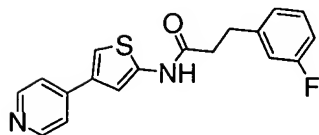
I-B-240



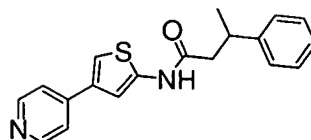
I-B-241



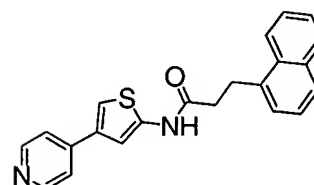
I-B-242



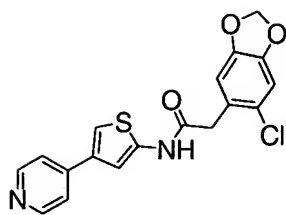
I-B-243



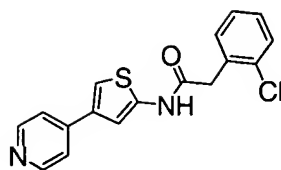
I-B-244



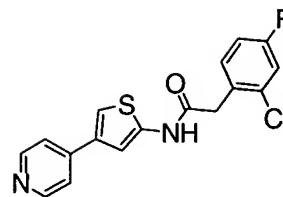
I-B-245



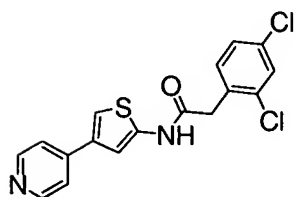
I-B-246



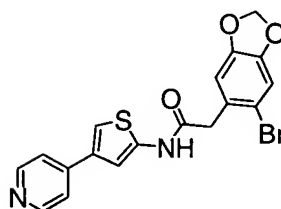
I-B-247



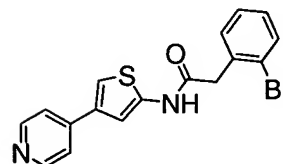
I-B-248



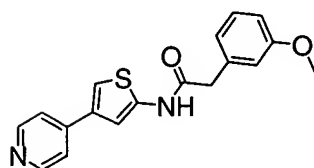
I-B-249



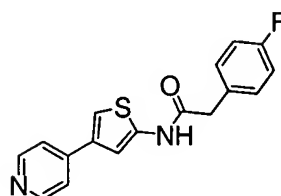
I-B-250



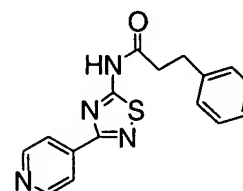
I-B-251



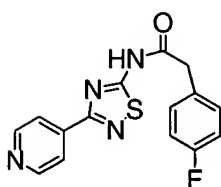
I-B-252



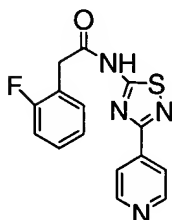
I-B-253



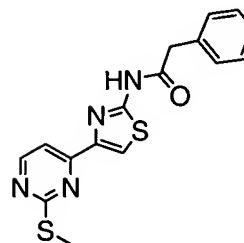
I-B-254



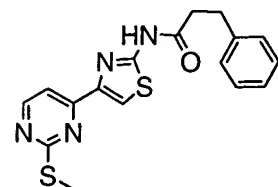
I-B-255



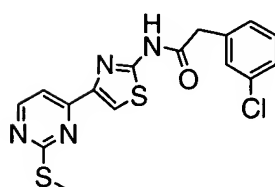
I-B-256



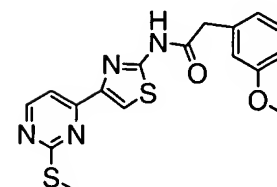
I-B-257



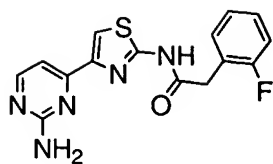
I-B-258



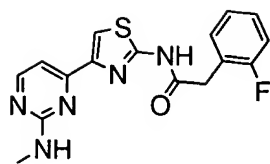
I-B-259



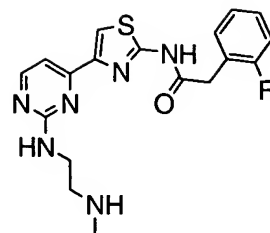
I-B-260



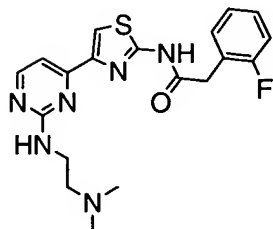
I-B-261



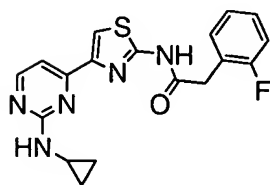
I-B-262



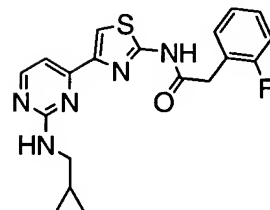
I-B-263



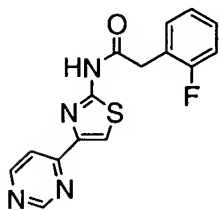
I-B-264



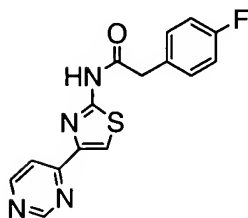
I-B-265



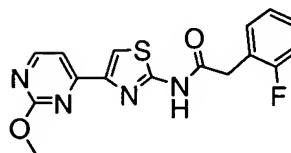
I-B-266



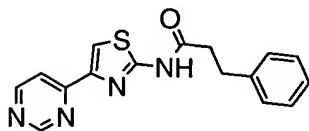
I-B-267



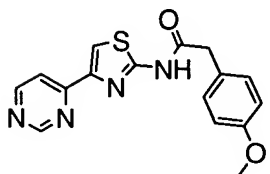
I-B-268



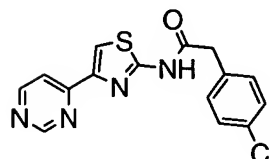
I-B-269



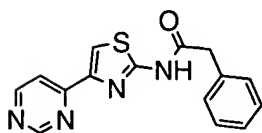
I-B-270



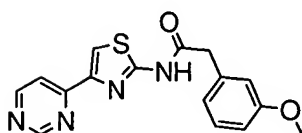
I-B-271



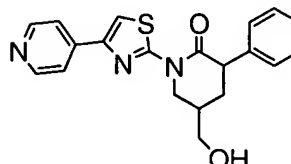
I-B-272



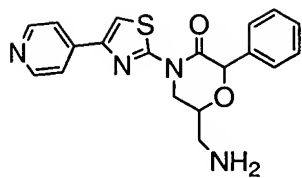
I-B-273



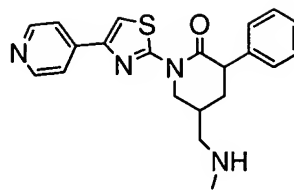
I-B-274



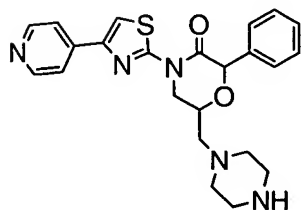
I-B-275



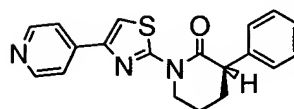
I-B-276



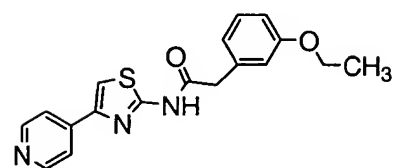
I-B-277



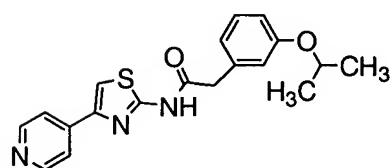
I-B-278



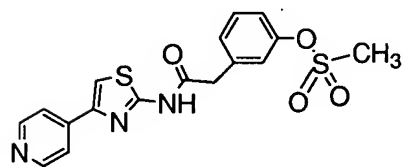
I-B-279



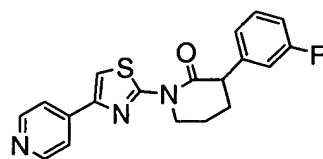
I-B-280



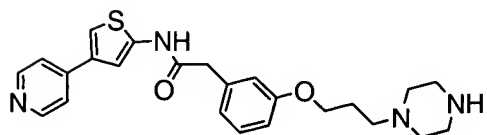
I-B-281



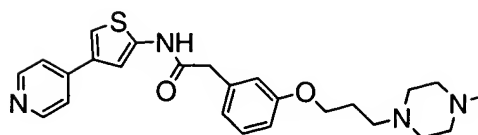
I-B-282



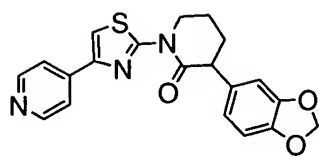
I-B-283



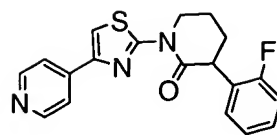
I-B-284



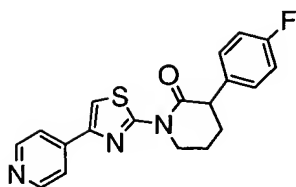
I-B-285



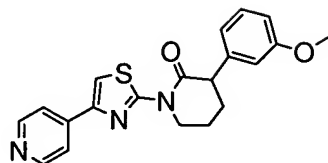
I-B-286



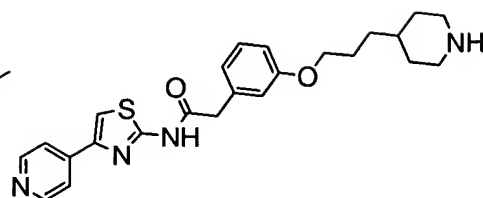
I-B-287



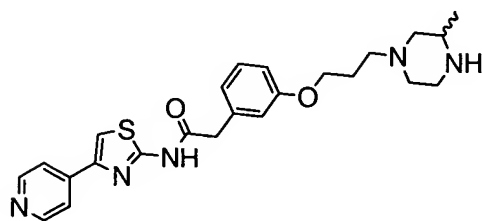
I-B-288



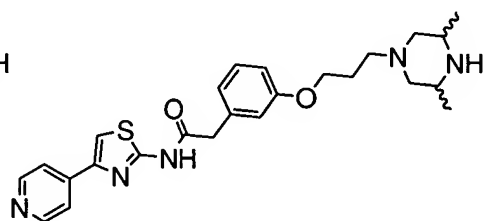
I-B-289



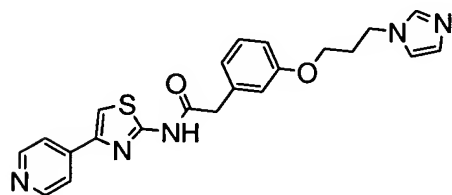
I-B-290



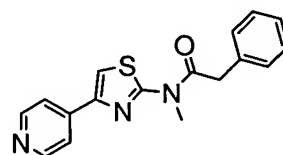
I-B-291



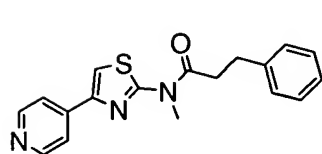
I-B-292



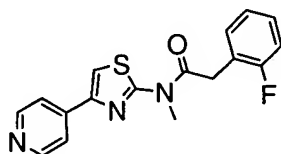
I-B-293



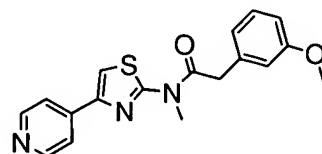
I-B-294



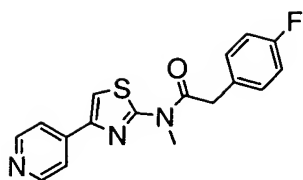
I-B-295



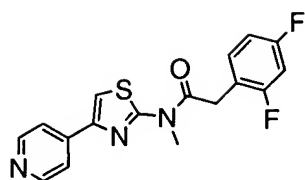
I-B-296



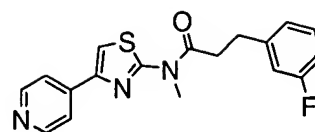
I-B-297



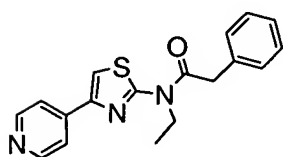
I-B-298



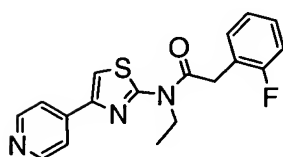
I-B-299



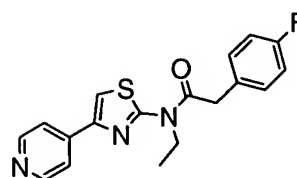
I-B-300



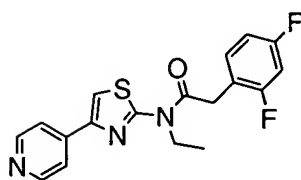
I-B-301



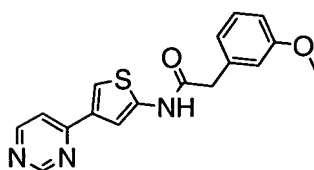
I-B-302



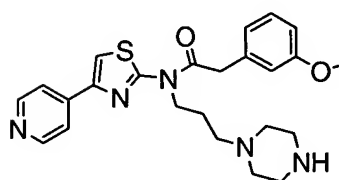
I-B-303



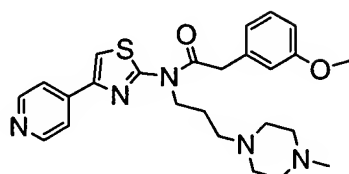
I-B-304



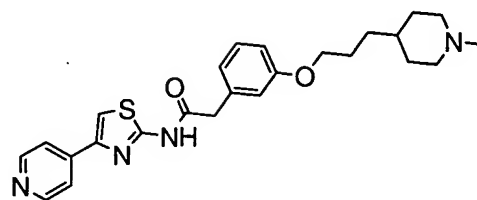
I-B-305



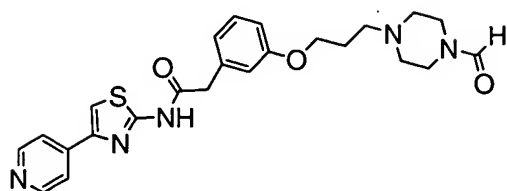
I-B-306



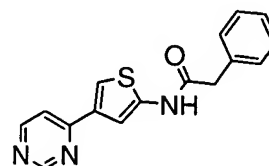
I-B-307



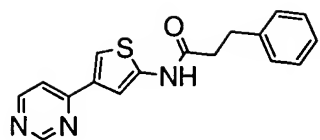
I-B-308



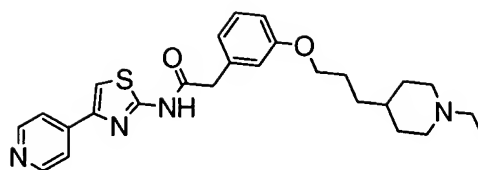
I-B-309



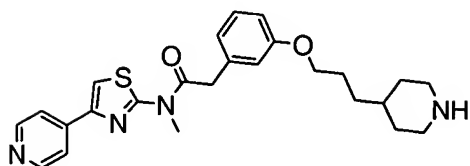
I-B-310



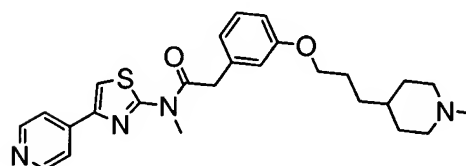
I-B-311



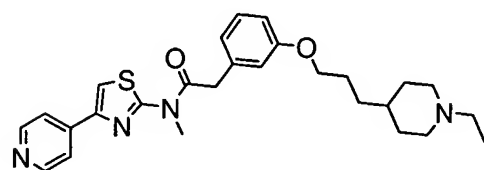
I-B-312



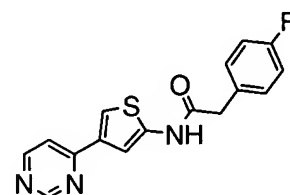
I-B-313



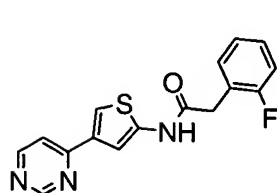
I-B-314



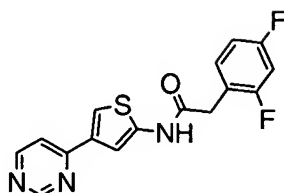
I-B-315



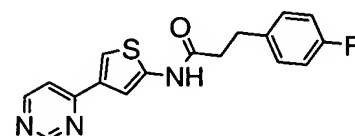
I-B-316



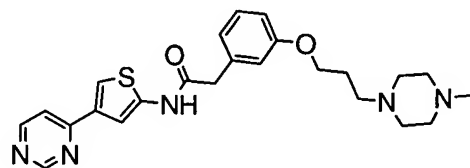
I-B-317



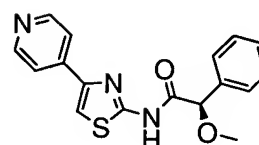
I-B-318



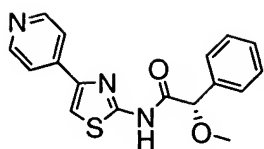
I-B-319



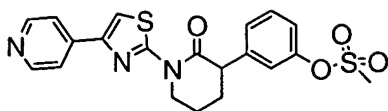
I-B-320



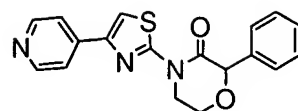
I-B-321



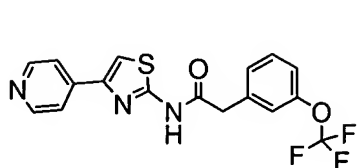
I-B-322



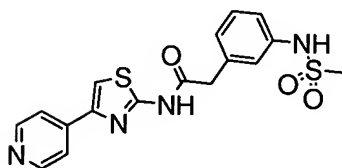
I-B-323



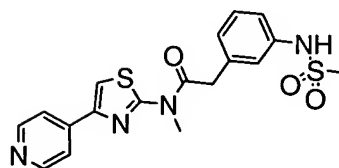
I-B-324



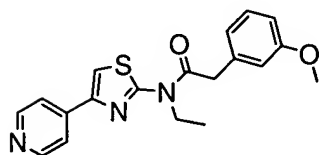
I-B-325



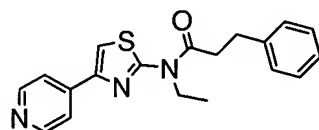
I-B-326



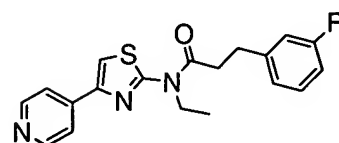
I-B-327



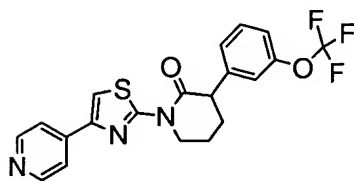
I-B-328



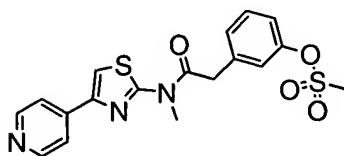
I-B-329



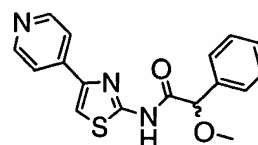
I-B-330



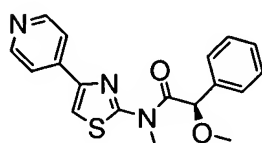
I-B-331



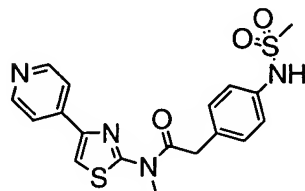
I-B-332



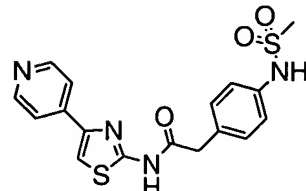
I-B-333



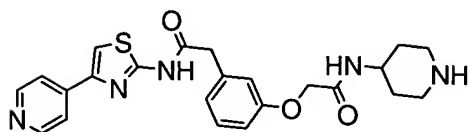
I-B-334



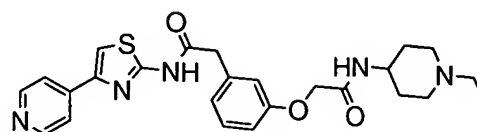
I-B-335



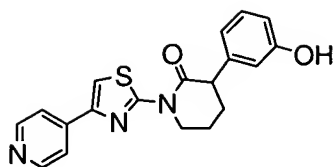
I-B-336



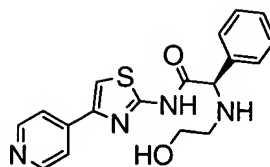
I-B-337



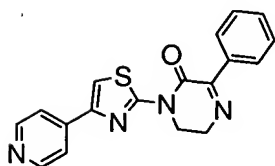
I-B-338



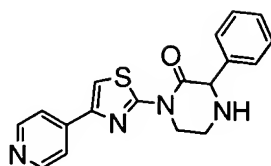
I-B-339



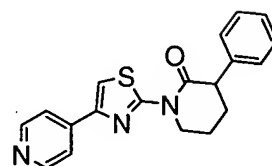
I-B-340



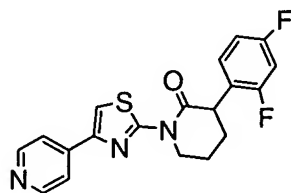
I-B-341



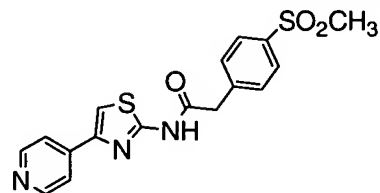
I-B-342



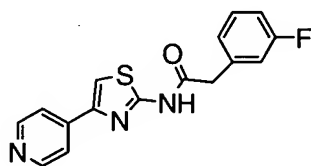
I-B-343



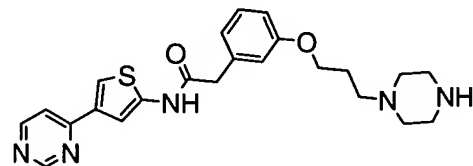
I-B-344



I-B-345



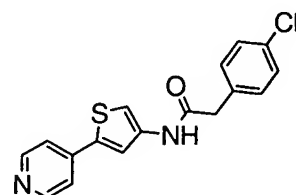
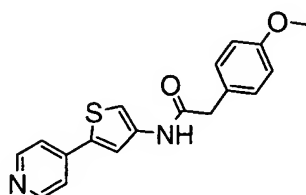
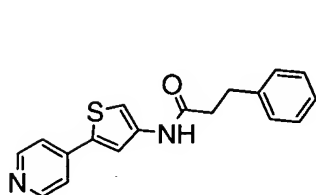
I-B-346

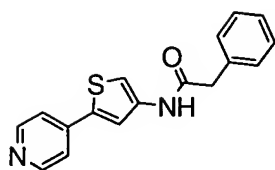
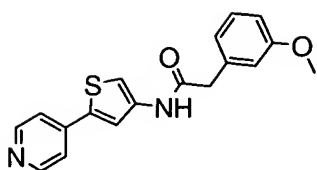
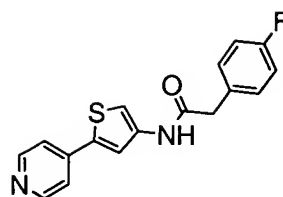
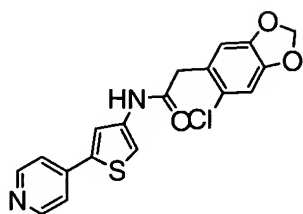
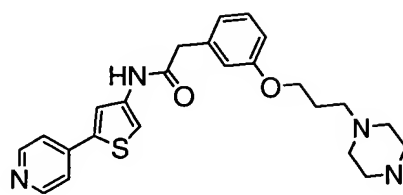
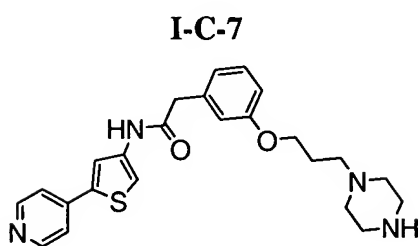
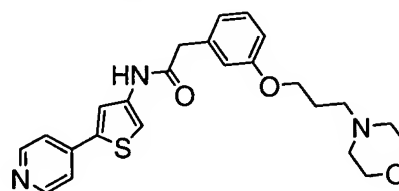
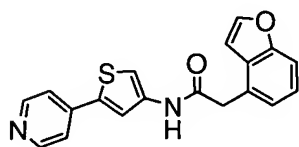
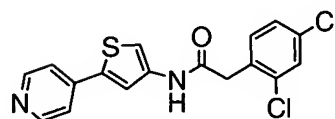
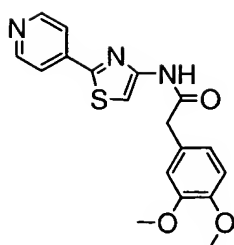
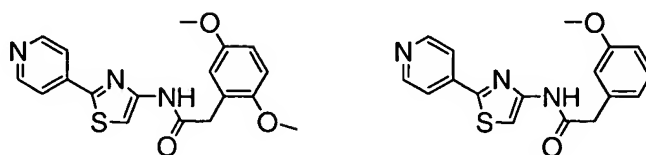


I-B-347

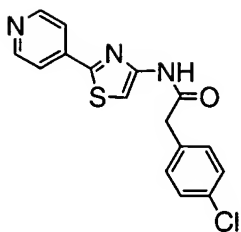
[0098] Representative examples of compounds of formula **I-C** are set forth below in Table 3 below.

[0099] Table 3. Examples of Compounds of Formula **I-C**:

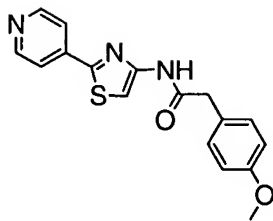


I-C-1**I-C-2****I-C-3****I-C-4****I-C-5****I-C-6****I-C-8****I-C-9****I-C-10****I-C-11****I-C-12**

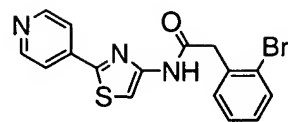
I-C-13



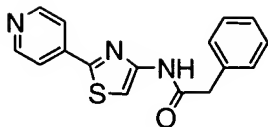
I-C-14



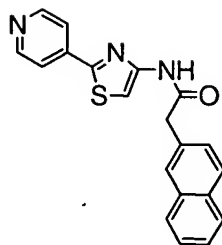
I-C-15



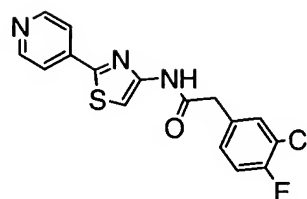
I-C-16



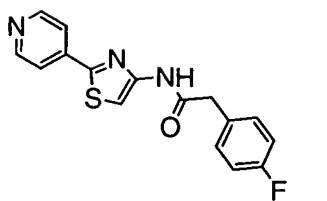
I-C-17



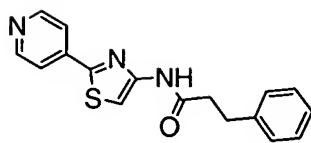
I-C-18



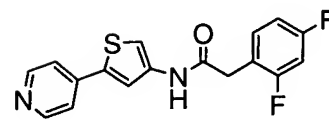
I-C-19



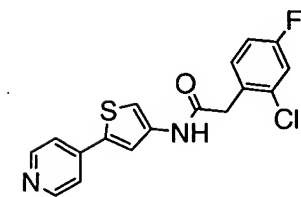
I-C-20



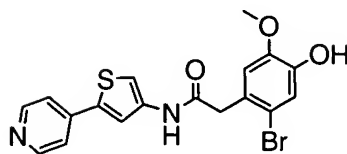
I-C-21



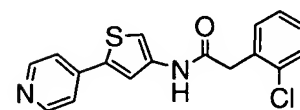
I-C-22



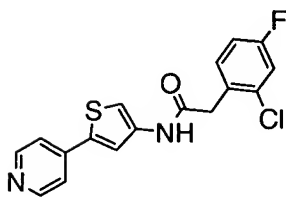
I-C-23



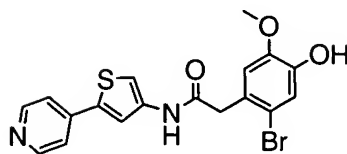
I-C-24



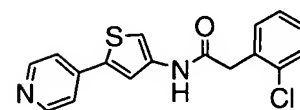
I-C-25

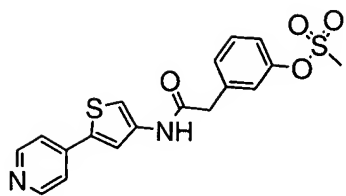


I-C-26

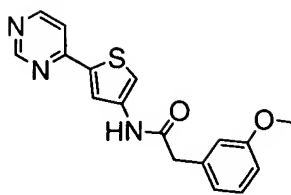


I-C-27

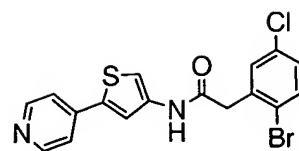




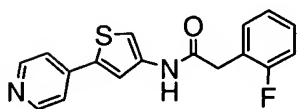
I-C-28



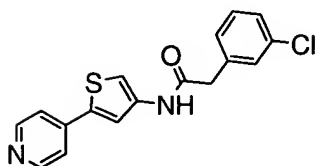
I-C-29



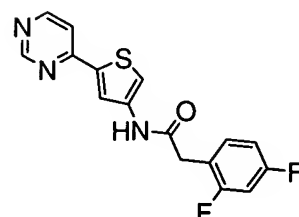
I-C-30



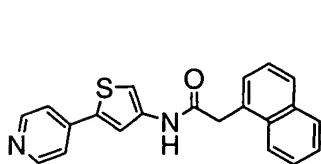
I-C-31



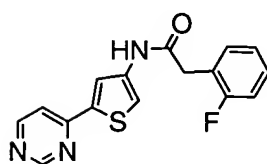
I-C-32



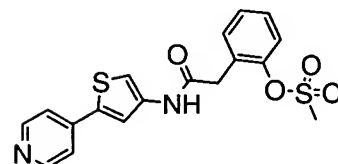
I-C-33



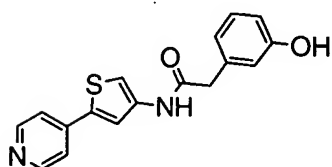
I-C-34



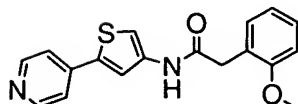
I-C-35



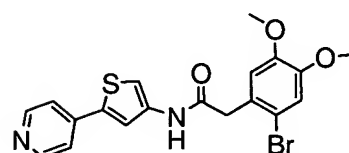
I-C-36



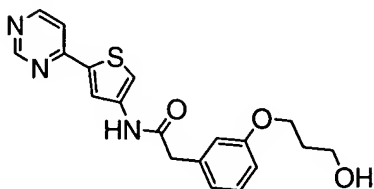
I-C-37



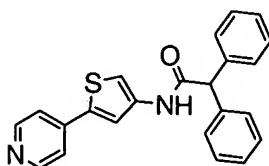
I-C-38



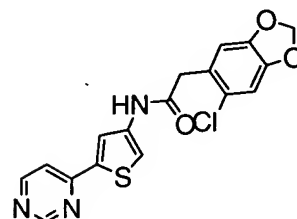
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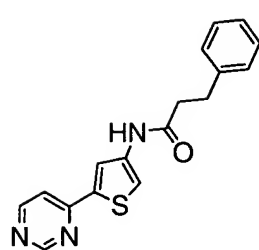
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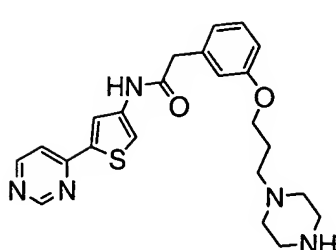
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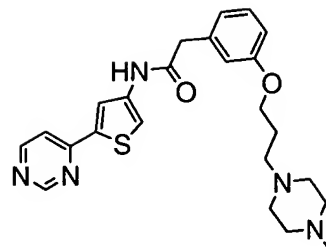
I-C-42



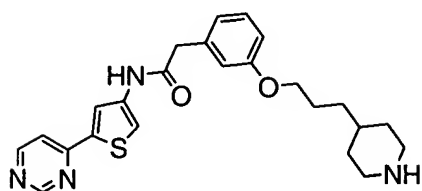
I-C-43



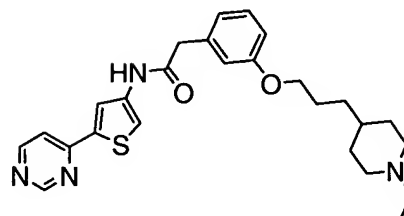
I-C-44



I-C-45



I-C-46

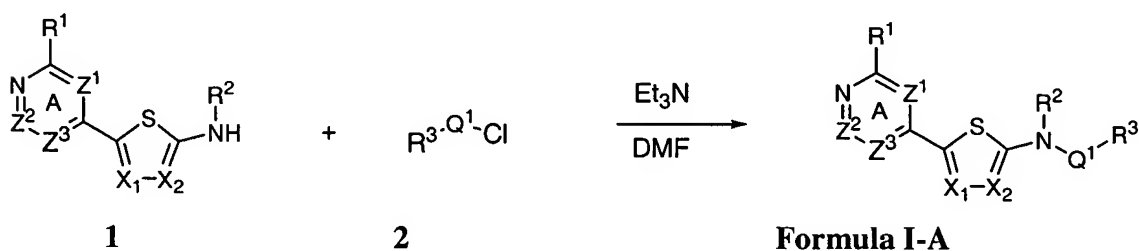


I-C-47

[00100] 4. General Synthetic Methodology:

[00101] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes below, and the preparative examples that follow.

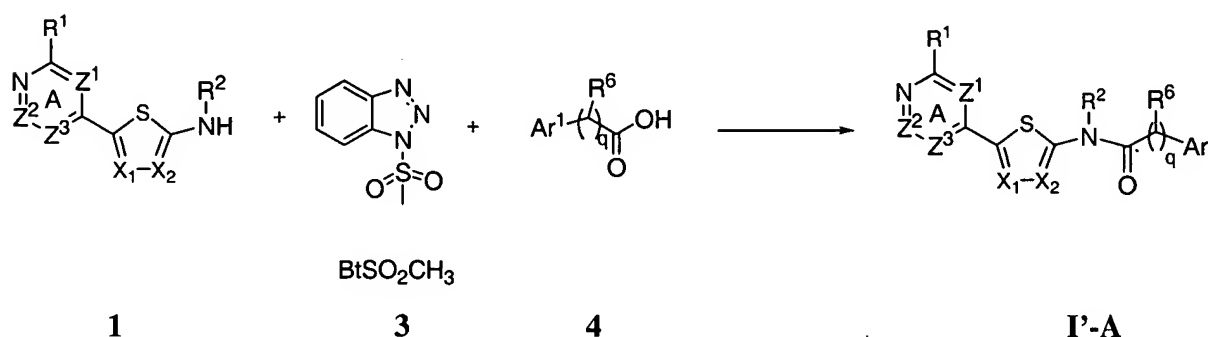
[00102] **Scheme I** below shows a general method for preparing compounds of formula **I-A**.



Scheme I

[00103] Specifically, as shown in **Scheme I**, the intermediate amine **1** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et₃N) to yield desired compounds of formula **I** as described generally and in classes, subclasses and species herein.

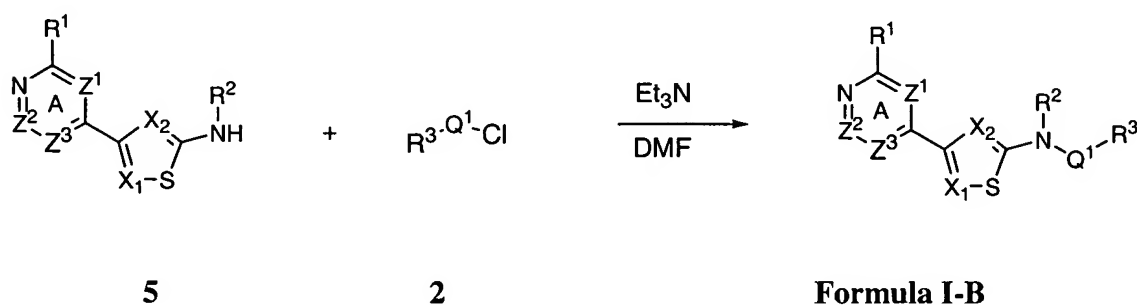
[00104] In certain embodiments, for compounds of formula **I-A**, Q^1 is CHR^6 , wherein R^6 is defined generally and in classes, subclasses and species herein. Scheme 2 below depicts a general procedure for the preparation of compounds where Q^1 is CHR^6 :



Scheme 2

[00105] Specifically, as shown in **Scheme 2**, the intermediate amine **1** is reacted with BtSO_2CH_3 **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-A** as described generally and in classes, subclasses and species herein.

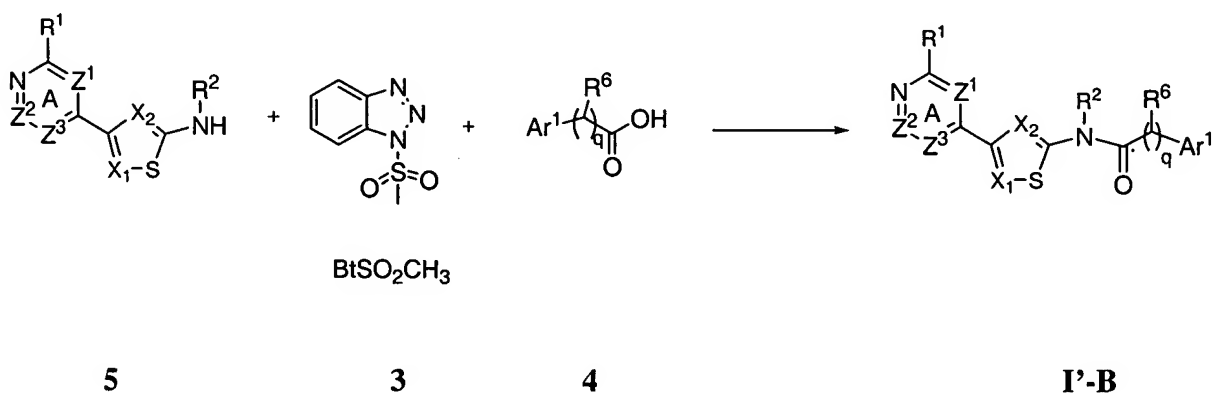
[00106] **Scheme 3** below shows a general method for preparing compounds of formula **I-B**.



Scheme 3

[00107] Specifically, as shown in **Scheme 3**, the intermediate amine **5** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et_3N) to yield desired compounds of formula **I-B** as described generally and in classes, subclasses and species herein.

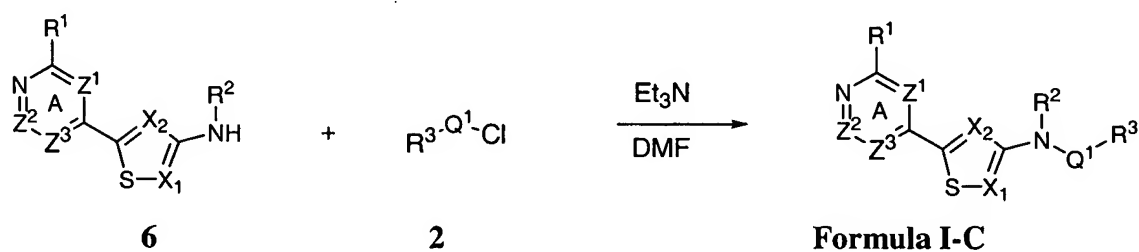
[00108] In certain embodiments, for compounds of formula **I-B**, Q^1 is CHR^6 , wherein R^6 is defined generally and in classes, subclasses and species herein. Scheme 4 below depicts a general procedure for the preparation of compounds where Q^1 is CHR^6 :



Scheme 4

[00109] Specifically, as shown in **Scheme 4**, the intermediate amine **5** is reacted with $BtSO_2CH_3$ **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-B** as described generally and in classes, subclasses and species herein.

[00110] **Scheme 5** below shows a general method for preparing compounds of formula **I-C**.

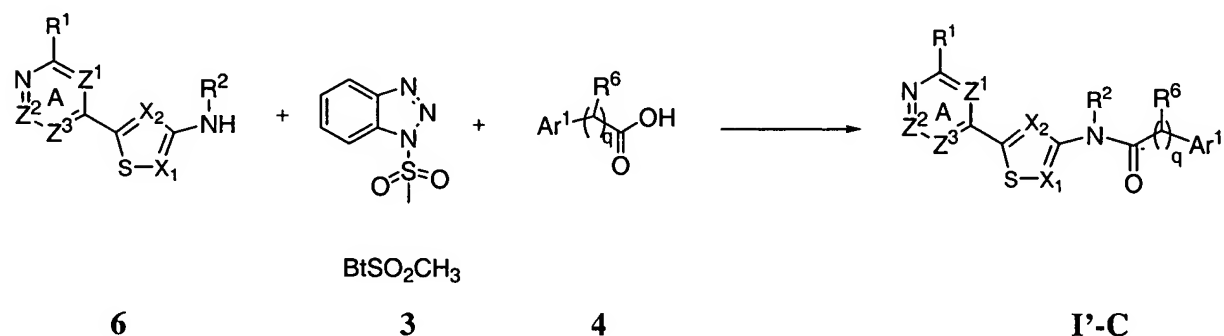


Scheme 5

[00111] Specifically, as shown in **Scheme 5**, the intermediate amine **6** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et_3N) to

yield desired compounds of formula **I-C** as described generally and in classes, subclasses and species herein.

[00112] In certain embodiments, for compounds of formula **I-C**, Q^1 is CHR^6 , wherein R^6 is defined generally and in classes, subclasses and species herein. Scheme 6 below depicts a general procedure for the preparation of compounds where Q^1 is CHR^6 :



Scheme 6

[00113] Specifically, as shown in **Scheme 6**, the intermediate amine **6** is reacted with BtSO_2CH_3 **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-C** as described generally and in classes, subclasses and species herein.

[00114] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials by methods generally available to one of ordinary skill in the art. Additional embodiments are exemplified in more detail herein.

[00115] *5. Uses, Formulation and Administration*

[00116] *Pharmaceutically acceptable compositions*

[00117] As discussed above, the present invention provides compounds that are inhibitors of protein kinases, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, psychotic disorders, an autoimmune disorder, a condition

associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. In preferred embodiments, the compounds are useful for the treatment of allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia (e.g., stroke), baldness, cancer, hepatomegaly, cardiovascular disease including cardiomegaly, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, inflammation, hypertension, angina pectoris, cerebrovascular contraction, peripheral circulation disorder, premature birth, arteriosclerosis, vasospasm (cerebral vasospasm, coronary vasospasm), retinopathy, erectile dysfunction (ED), AIDS, osteoporosis, Crohn's Disease and colitis, neurite outgrowth, and Raynaud's Disease. In preferred embodiments, the disease, condition, or disorder is atherosclerosis, hypertension, erectile dysfunction (ED), reperfusion/ischemia (e.g., stroke), or vasospasm (cerebral vasospasm and coronary vasospasm).

[00118] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00119] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00120] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of

this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB).

[00121] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N⁺(C₁₋₄alkyl)₄ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00122] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle,

which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00123] *Uses of Compounds and Pharmaceutically acceptable compositions*

[00124] In yet another aspect, a method for the treatment or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00125] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00126] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00127] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00128] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00129] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00130] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00131] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00132] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00133] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00134] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper

medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00135] As described generally above, the compounds of the invention are useful as inhibitors of protein kinases. In one embodiment, the compounds and compositions of the invention are inhibitors of one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB), and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) is implicated in the disease, condition, or disorder. When activation of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as “ROCK, ERK, GSK, AGC (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) -mediated disease” or disease symptom. Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) is implicated in the disease state.

[00136] The activity of a compound utilized in this invention as an inhibitor of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB), may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB). Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB). Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/ ROCK, inhibitor/ERK, inhibitor/GSK kinase, or inhibitor/AGC (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated

with ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) bound to known radioligands.

[00137] The term “measurably inhibit”, as used herein means a measurable change in ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) activity between a sample comprising said composition and a ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) kinase and an equivalent sample comprising ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) kinase in the absence of said composition.

[00138] The terms “AKT-mediated disease” or “AKT-mediated condition”, as used herein, mean any disease or other deleterious condition in which AKT is known to play a role. The terms “AKT-mediated disease” or “AKT-mediated condition” also mean those diseases or conditions that are alleviated by treatment with a AKT inhibitor. AKT-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, and neurodegenerative disorders. The association of AKT, also known as protein kinase B, with various diseases has been described [Khwaja, A. *Nature* **1999**, *401*, 33-34; Yuan, Z.Q. *et al.*, *Oncogene* **2000**, *19*, 2324-2330; Namikawa, K. *et al.*, *The Journal of Neuroscience* **2000**, *20*, 2875-2886].

[00139] The term “PDK1-mediated condition” or “disease”, as used herein, means any disease or other deleterious condition in which PDK1 is known to play a role. The term “PDK1-mediated condition” or “disease” also means those diseases or conditions that are alleviated by treatment with a PDK1 inhibitor. PDK1-mediated diseases or conditions include, but are not limited to, proliferative disorders, and cancer. Preferably, said cancer is selected from pancreatic, prostate, or ovarian cancer.

[00140] The term “PKA-mediated condition” or “disease”, as used herein, means any disease or other deleterious condition in which PKA is known to play a role. The term “PKA-mediated condition” or “disease” also means those diseases or conditions that are alleviated by treatment with a PKA inhibitor. PKA-mediated diseases or conditions include, but are not limited to, proliferative disorders and cancer.

[00141] The term “p70^{S6K}-mediated condition” or “disease”, as used herein, means any disease or other deleterious condition in which p70^{S6K} is known to play a role. The term “p70S6K-mediated condition” or “disease” also means those diseases or conditions that are

alleviated by treatment with a p70^{S6K} inhibitor. p70^{S6K}-mediated diseases or conditions include, but are not limited to, proliferative disorders, such as cancer and tuberous sclerosis.

[00142] The terms “ERK-mediated disease” or “ERK-mediated condition”, as used herein mean any disease or other deleterious condition in which ERK is known to play a role. The terms “ERK-2-mediated disease” or “ERK-2-mediated condition” also mean those diseases or conditions that are alleviated by treatment with an ERK-2 inhibitor. Such conditions include, without limitation, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer’s disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders, and hormone-related diseases. The term “cancer” includes, but is not limited to the following cancers: breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin’s, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. ERK-2 protein kinase and its implication in various diseases has been described [Bokemeyer *et al.*, *Kidney Int.* **1996**, 49, 1187; Anderson *et al.*, *Nature* **1990**, 343, 651; Crews *et al.*, *Science* **1992**, 258, 478; Bjorbaek *et al.*, *J. Biol. Chem.* **1995**, 270, 18848; Rouse *et al.*, *Cell* **1994**, 78, 1027; Raingeaud *et al.*, *Mol. Cell Biol.* **1996**, 16, 1247; Chen *et al.*, *Proc. Natl. Acad. Sci. USA* **1993**, 90, 10952; Oliver *et al.*, *Proc. Soc. Exp. Biol. Med.* **1995**, 210, 162; Moodie *et al.*, *Science* **1993**, 260, 1658; Frey and Mulder, *Cancer Res.* **1997**, 57, 628; Sivaraman *et al.*, *J Clin. Invest.* **1997**, 99, 1478; Whelchel *et al.*, *Am. J. Respir. Cell Mol. Biol.* **1997**, 16, 589].

[00143] The term “GSK-3-mediated disease” as used herein, means any disease or other deleterious condition or disease in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, autoimmune diseases, inflammatory diseases, metabolic, neurological and neurodegenerative diseases (e.g., Alzheimer’s disease, Huntington’s disease, Parkinson’s disease and basal ganglia movement disorders, chorea, dystonia, Wilson Disease, Pick Disease, frontal lobe degeneration, progressive supranuclear palsy (PSP), Creutzfeldt-Jakob

Disease, tauopathy and corticobasal degeneration (CBD)), psychotic disorders (e.g., schizophrenia, AIDS-associated dementia, depression, bipolar disorder, and anxiety disorders), cardiovascular diseases, allergy, asthma, diabetes, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), multiple sclerosis (MS), cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, and baldness.

[00144] The term "ROCK-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which ROCK is known to play a role. The term "ROCK-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ROCK inhibitor. Such conditions include, without limitation, hypertension, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, cancer, erectile dysfunction, arteriosclerosis, spasm (cerebral vasospasm and coronary vasospasm), retinopathy (e.g., glaucoma), inflammatory disorders, autoimmune disorders, AIDS, osteoporosis, myocardial hypertrophy, ischemia/reperfusion-induced injury, and endothelial dysfunction.

[00145] In other embodiments, the invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula I. This method is especially useful for diabetic patients.

[00146] In yet another embodiment, the invention relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula I. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

[00147] In still another embodiment, the invention relates to a method of inhibiting the phosphorylation of β -catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula I. This method is especially useful for treating schizophrenia.

[00148] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures.

The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00149] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, For example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents of the present invention include surgery, radiotherapy (in but a few examples, gamma.-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabine, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies see, <http://www.nci.nih.gov/>, a list of the FDA approved oncology drugs at <http://www.fda.gov/cder/cancer/druglistframe.htm>, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

[00150] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Exelon®;

treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex[®] and Rebif[®]), Copaxone[®], and mitoxantrone; treatments for asthma such as albuterol and Singulair[®]; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00151] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00152] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device.

[00153] Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00154] Another aspect of the invention relates to inhibiting ROCK, ERK, GSK, or AGC (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

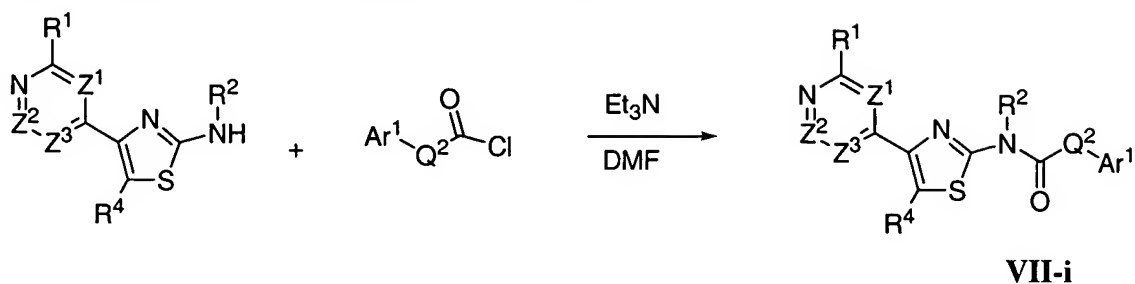
[00155] Inhibition of ROCK, ERK, GSK, or AGC (e.g., PKA, PDK, p70^{S6K}-1 and -2, and PKB) kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

EXAMPLES

[00156] GENERAL EXPERIMENTAL PROCEDURES:

[00157] As depicted in Schemes 7, 8, 9, 10, and 11 below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that although the general methods depict the synthesis of compounds of general formula VII, the following general methods can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

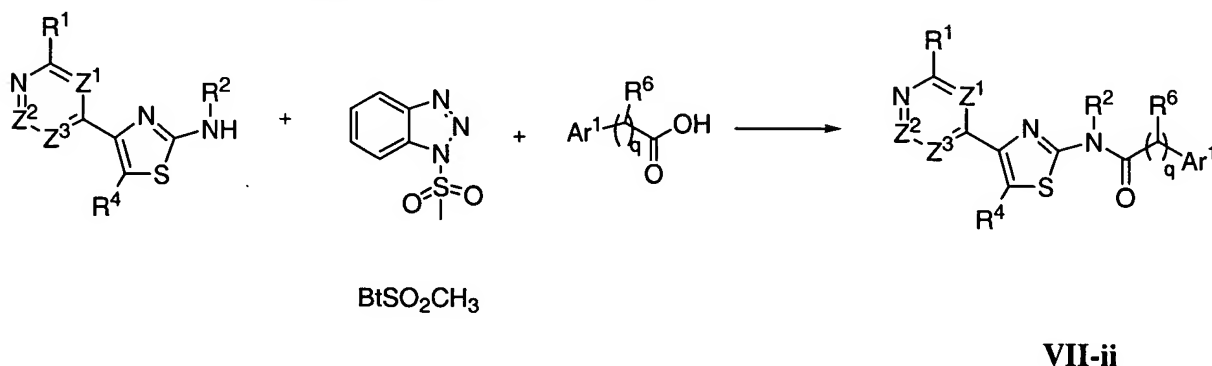
[00158] General Method A: Acylation of amines



Scheme 7

0.25 mmol of amine, and 0.5 mmol of acid chloride were dissolved in 2 mL of anhydrous DMF. 0.75 mmol of Et₃N was then added to the reaction mixture, and the mixture was stirred at RT for overnight. After completion of the reaction, EtOAc was added, the organic layer was washed with H₂O and brine, and was then dried over Na₂SO₄. Removal of the solvent gave a solid, **VII-i**, which was further purified by preparative HPLC.

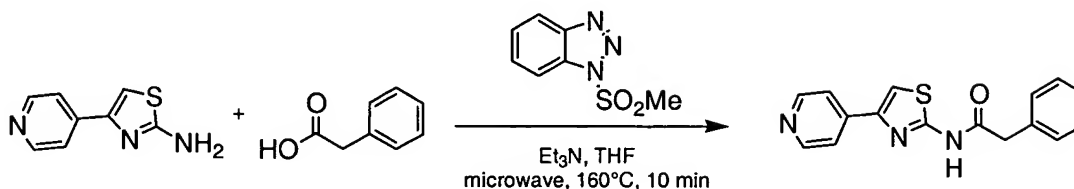
[00159] General Method B: Acylation of amines



Scheme 8

A mixture of BtSO₂CH₃ (preparation described below) (0.25 mmol), acid (0.25 mmol), and Et₃N (0.35mmol) was refluxed in dry THF for about 20 min. Amine (0.25 mmol) was then added to the reaction mixture, and the mixture was refluxed for 18 h. After the mixture was concentrated, EtOAc (5 mL) was added, and the organic phase was washed with 2 M NaOH and dried over anhydrous MgSO₄. Removal of the solvent gave a solid, **VII-ii**, which was purified by preparative HPLC.

[00160] General Method C: Acylation of amines

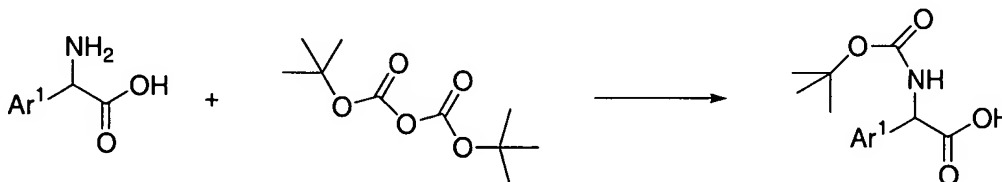


Scheme 9

[00161] Amine (1 mmol), carboxylic acid (1.2 mmol) and Bt-SO₂Me (1.2 mmol) are combined in a microwave reaction vessel. Anhydrous THF (2 mL) is added followed by triethylamine (2 mmol) and the mixture heated by microwave irradiation at 160°C for 10 minutes. Product is isolated by precipitation following addition of acetonitrile, or by preparative HPLC.

[00162] Standard protection and deprotection of amino and hydroxyl functionalities:

[00163] General Method D: Protection of amino groups



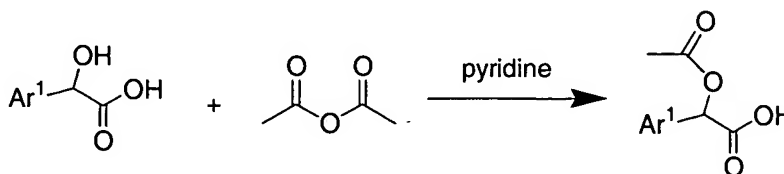
Scheme 10

[00164] 0.25 mmol of amine, 0.25 mmol of Boc anhydride were mixed in 2 mL of anhydrous CH₂Cl₂. To the reaction mixture, 0.75 mmol of Et₃N was added and the mixture was stirred at RT for overnight. The solvent was evaporated to give the Boc protected amine.

[00165] General Method E: Deprotection of Boc-protected amines

[00166] To the Boc protected amine (0.25 mmol) in a vial, 2 mL 4N HCl in dioxane was added and the reaction mixture was stirred at RT for 30 min. The solvent was evaporated to give the free amine product.

[00167] General Method F: Protection of phenols and alcohols



Scheme 11

[00168] Hydroxy acid (2.5 mol) was stirred with acetic anhydride (0.57 mL, 6 mol) in pyridine (5mL) overnight and then evaporated in vacuo. The resulting oil was partitioned between EtOAc and 1N HCl and the resulting organic layer washed successively with 1 N HCl, water and brine, dried over MgSO₄, and evaporated to dryness.

[00169] General Method G: Deprotection of acetylated phenols and alcohols

[00170] The acetyl-protected alcohol or phenol (0.25 mmol) was dissolved in EtOH, 0.5 mL 2N NaOH was added and the mixture was stirred at RT for 1h. The solvent was evaporated and redissolved in DMF/CH₃CN/H₂O, and subjected to preparative HPLC for purification.

[00171] General Method H: Preparation of phenylacetic acids

[00172] Substituted benzaldehyde (5 mmol) and zinc iodide (10 mg) were dissolved or suspended in anhydrous acetonitrile (5 – 10 mL). Trimethylsilyl cyanide (12 mmol) was added dropwise and the mixture stirred at room temperature overnight. The mixture was rotary evaporated and the residue dissolved in glacial acetic acid (2 mL) and concentrated hydrochloric acid (3 mL). Tin (II) chloride dihydrate (12 mmol) was added and the mixture heated to reflux for 1 – 2 hours. To the cooled mixture was added water (20 mL) and the mixture was extracted with methylene chloride (3 x 15 mL). The extracts were washed with water (x 2) and brine and dried over MgSO₄. The solution is concentrated and the product precipitated by addition of hexane.

[00173] General Method I: Preparation of α -hydroxyphenylacetic acids

[00174] Substituted benzaldehyde (5 mmol) and zinc iodide (10 mg) were dissolved or suspended in anhydrous acetonitrile (5 – 10 mL). Trimethylsilyl cyanide (12 mmol) was added dropwise and the mixture stirred at room temperature overnight. The mixture was rotary evaporated and the residue dissolved in glacial acetic acid (2 mL) and concentrated hydrochloric acid (3 mL) and the mixture heated to reflux for 1 – 2 hours. To the cooled mixture was added water (20 mL) and the mixture was extracted with methylene chloride (3 x 15 mL). The extracts were washed with water (x 2) and brine and dried over MgSO₄. The solution is concentrated and the product precipitated by addition of hexane.

[00175] Although the preparation of certain amines are described below, it will be appreciated that a variety of alternate amines can be prepared as described generally below and can be utilized in the preparation of compounds of the invention.

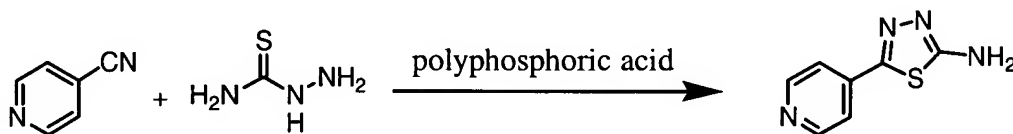
[00176] EXPERIMENTAL PROCEDURES:

[00177] Preparation of N-(1-Methanesulfonyl)benzotriazole (BtSO₂CH₃):

[00178] To an ice-cold solution of benzotriazole (11.9g, 0.10 mol) and pyridine (12.0 g, 0.16 mol) in dry toluene (120 mL) was added methanesulfonyl chloride (9.3 mL, 0.12 mol) in toluene (30 mL) dropwise. The mixture was then stirred overnight at room temperature. EtOAc (150 mL) and H₂O (100 mL) were added, the organic layer was separated, successively washed with water and brine, and dried over anhydrous MgSO₄. Removal of solvents in vacuo gave BtSO₂CH₃ as a white solid.

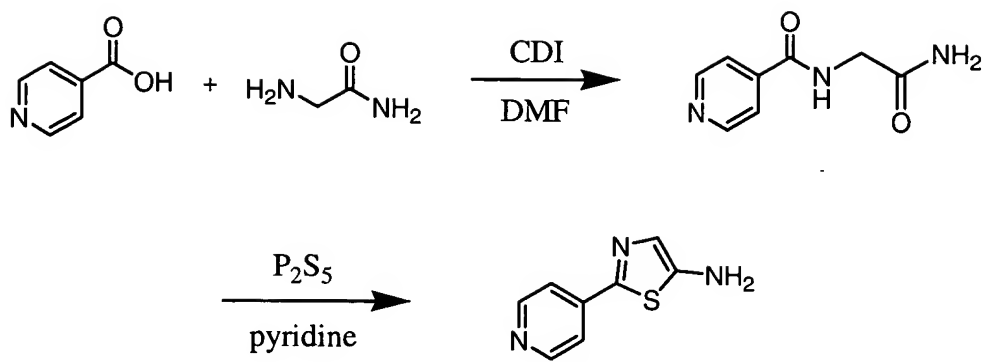
[00179] The synthesis of certain exemplary amines (described generally above) are described more specifically below. It will be appreciated that a variety of alternate amines can be prepared according to methods known in the art and can be utilized in the preparation of compounds of the invention.

[00180] Preparation of 5-Pyridin-4-yl-[1,3,4]thiadiazol-2-ylamine



[00181] A mixture of 4-cyanopyridine (5.2 g, 50 mmol) and thiosemicarbazide (6.37 g, 70 mmol) was heated in polyphosphoric acid at 100°C overnight. The reaction mixture was poured onto 200 g ice and the pH was adjusted to approximately 7.5 by addition of 6N NaOH. The product precipitated and was filtered and dried to afford 5-pyridin-4-yl-[1,3,4]thiadiazol-2-ylamine (4.59 g, 51%). ¹H NMR CD₃OD: 7.8 (d, 2H), 8.62 (d, 2H).

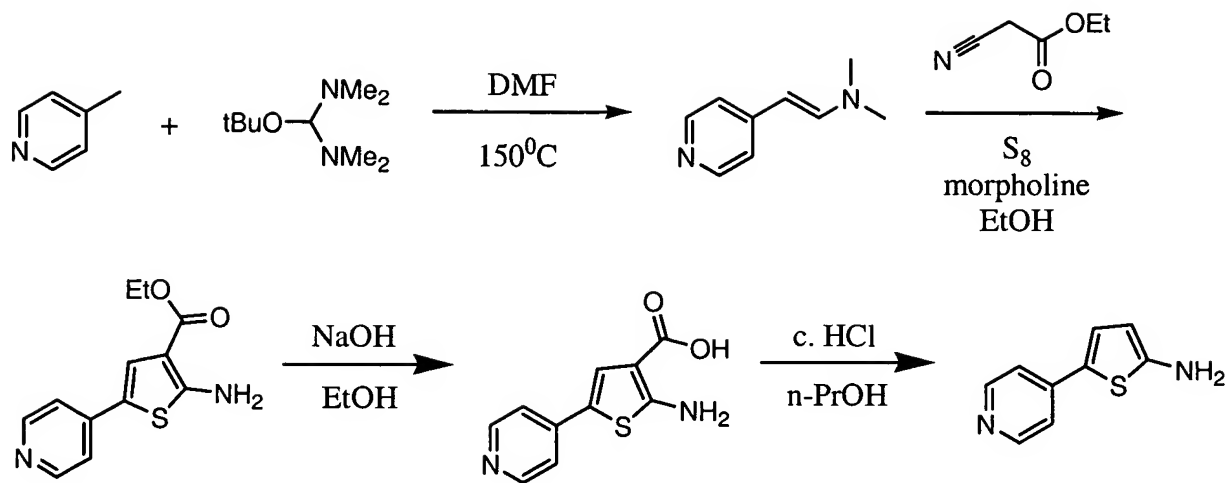
[00182] Preparation of 2-Pyridin-4-yl-thiazol-5-ylamine



[00183] N-Carbamoylmethyl-isonicotinamide: To 200 mL DMF was added isonicotinic acid (12.3 g, 0.1mol), and carbonyl diimidazole. The mixture was stirred at room temperature for 1h then glycineamide hydrochloride and 200 mL THF were added and the mixture was stirred overnight. To the mixture was added 300 mL acetonitrile to precipitate the product, which was filtered, washed and dried to afford N-carbamoylmethyl-isonicotinamide (13.0 g, 72.6%). ¹H NMR d⁶-DMSO: 3.85 (d, 2H), 7.08 (br s, 1H), 7.46 (br s, 1H), 7.8 (d, 2H), 8.73 (d, 2H), 9.0 (br, 1H).

[00184] 2-Pyridin-4-yl-thiazol-5-ylamine: A mixture of N-carbamoylmethyl-isonicotinamide (10.8 g, 0.06mol), and phosphorus pentasulfide (13.40 g, 0.06mol) in pyridine (250 mL) was heated at 100°C for 6h. The mixture was poured into to NaHCO₃ aqueous solution, the product was extracted into ethyl acetate, the solvent was removed under reduced pressure, the product was purified by silica gel flash chromatography to afford 2-pyridin-4-yl-thiazol-5-ylamine in 20% yield. ¹H NMR d₆-DMSO: 6.36 (s, 2H), 6.95 (s, 1H), 7.59 (d, 2H), 8.54 (d, 2H).

[00185] Preparation of 5-Pyridin-4-yl-thiophen-2-ylamine



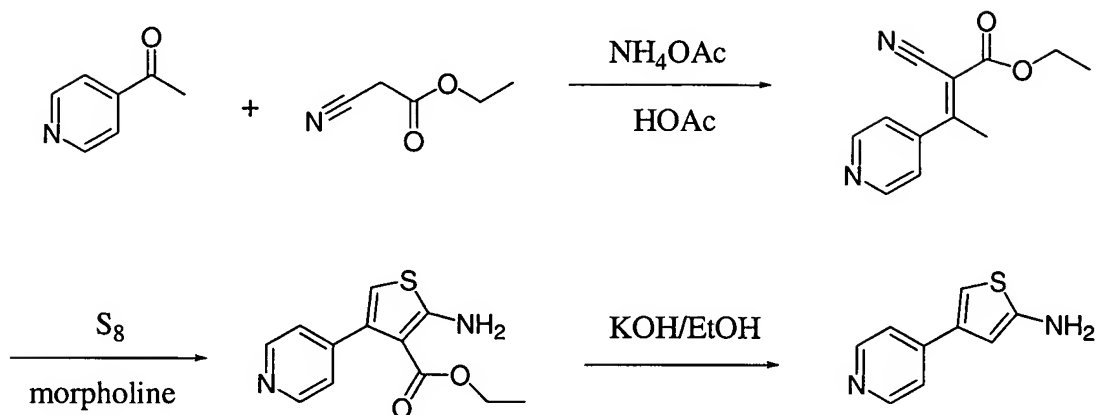
[00186] Dimethyl-(2-pyridin-4-yl-vinyl)-amine: 4-Methyl-pyridine (50 mmol) and Brederick's reagent (C-tert-Butoxy-N,N,N',N'-tetramethyl-methanediamine, 62.5 mmol) were dissolved in 12.5 mL of DMF in a sealed tube and the reaction mixture was heated to 150°C overnight. The solvent was evaporated to give a brown solid that was carried on to the next step.

[00187] 2-Amino-5-pyridin-4-yl-thiophene-3-carboxylic acid ethyl ester: A stirred solution of dimethyl-(2-pyridin-4-yl-vinyl)-amine and ethyl cyanoacetate (50 mmol) in 60 mL EtOH was treated with 50 mmol of elemental sulfur and 2 mL morpholine at room temperature and stirred overnight. Precipitation formed. Cooled to -20°C and filtered off the solid, washed with hexane to give yellow solid. (60% yield). ^1H NMR CDCl_3 : 8.48 (2H, m), 7.50 (1H, s), 7.29 (2H, m), 6.30 (2H, br), 4.32 (2H, q), 1.37 (3H, t).

[00188] 2-Amino-5-pyridin-4-yl-thiophene-3-carboxylic acid: To 2-amino-5-pyridin-4-yl-thiophene-3-carboxylic acid ethyl ester (1 mmol) in 4 mL EtOH was added 1 mL 2N NaOH and the reaction mixture was refluxed for 2 hours, then cooled to room temperature. A precipitate formed, which was filtered. The filtrate was diluted with 2 mL H_2O and neutralized with dilute H_2SO_4 until more precipitate formed. The mixture was cooled and the solid filtered. The combined solids were used without further purification. MS $[\text{M}+\text{H}] = 221$. ^1H NMR CD_3OD : 8.22 (2H, m), 7.83 (1H, s), 7.65 (2H, m).

[00189] 5-Pyridin-4-yl-thiophen-2-ylamine: 2-Amino-5-pyridin-4-yl-thiophene-3-carboxylic acid was dissolved in 4 mL of n-propanol, 2 mL of conc. HCl was added and the reaction mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled and the solid filtered, to give 5-pyridin-4-yl-thiophen-2-ylamine as a yellow solid (82%). MS $[\text{M}+\text{H}] = 177$.

[00190] Preparation of 4-Pyridin-4-yl-thiophen-2-ylamine:



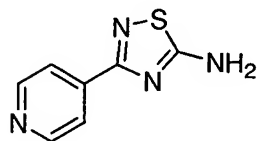
Scheme 12

[00191] 2-Cyano-3-pyridin-4-yl-but-2-enoic acid ethyl ester: Ethyl cyanoacetate (60 mmol, 6.78 g) and 4-pyridylacetophenone (60 mmol, 7.26g) were dissolved in 35 mL of dry benzene to which 7 mmol of ammonium acetate and 1.5 mL glacial acetic acid were added. The mixture was refluxed under a Dean-Stark trap until the formation of H₂O ceased. The mixture was cooled, diluted with benzene, and washed with H₂O. The organic layer was dried with Na₂SO₄, filtered, and concentrated in vacuo. The reaction mixture was carried on for next step without purification.

[00192] 2-Amino-4-pyridin-4-yl-thiophene-3-carboxylic acid ethyl ester. To a stirred solution of 2-Cyano-3-pyridin-4-yl-but-2-enoic acid ethyl ester in 100mL EtOH was added 60 mmol of sulfur and 1 mL morpholine. The mixture was stirred at room temperature overnight. The precipitate was filtered, washed with cold EtOH and hexane to give a light yellow solid. The filtrate was concentrated and redissolved in cold ethanol, filtered and washed with hexane to give more product. Overall yield is 60%. NMR 500MHz, CDCl₃: 8.57 (2H, m), 7.31 (2H, m), 6.25 (2H, br), 6.17 (1H, s), 4.10 (2H, q), 0.99 (3H, t).

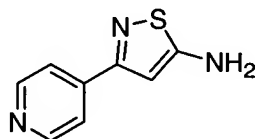
[00193] 4-Pyridin-4-yl-thiophen-2-ylamine: 2.49g of 2-Amino-4-pyridin-4-yl-thiophene-3-carboxylic acid ethyl ester (10 mmol) was dissolved into a mixture of 10 mL 20% KOH and EtOH (10 mL) and the reaction mixture was refluxed for 18 hours. The mixture was cooled to room temperature and 10 mL H₂O was added and the mixture was stirred at room temperature overnight. The precipitate was filtered, washed with H₂O, and dried. To afford the product as a light yellow solid (65% yield). NMR 500MHz, CD₃OD: 8.45 (2H, m), 7.60 (2H, m), 7.07 (1H, s), 6.54 (1H, s).

[00194] Preparation of 3-Pyridin-4-yl-[1,2,4]thiadiazol-5-ylamine

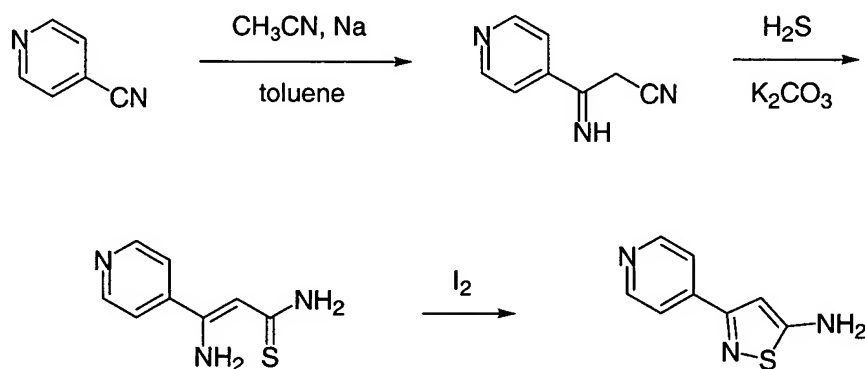


[00195] 3-Pyridin-4-yl-[1,2,4]thiadiazol-5-ylamine was prepared as described in EP 0455356. NMR 500MHz, d6-DMSO: 8.7 (br s, 2H), 8.2 (br s, 2H), 7.9 (m, 2H).

[00196] Preparation of 3-Pyridin-4-yl-isothiazol-5-ylamine

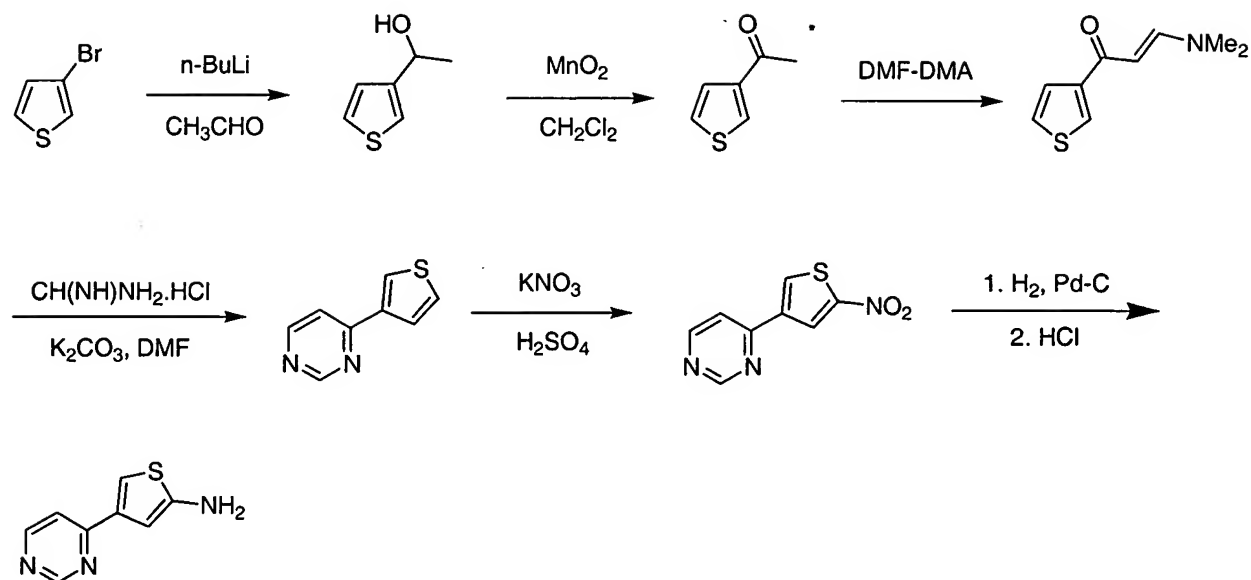


[00197] 3-Pyridin-4-yl-isothiazol-5-ylamine was prepared according to the following scheme as described in EP129407.



Scheme 13

[00198] Preparation of 4-Pyrimidin-4-yl-thiophen-2-ylamine



Scheme 14

[00199] 1-(3-Thienyl)-ethanol. In a 3 L four-necked round-bottomed flask equipped with an overhead stirrer, addition funnel, and low-temperature thermometer, 202.4 g (1.24 mol) of 3-bromothiophene was dissolved in 1L of 10% THF-hexane. The solution was cooled to -10°C using a dry-ice/acetone bath. n-BuLi was added dropwise via the addition funnel. A white solid precipitated during the addition. The reaction was stirred for one hour and 80 mL (excess) of acetaldehyde was added. The reaction was stirred for 10 minutes, poured into 1N HCl and extracted with diethyl ether. The extract was dried (MgSO_4) and filtered over a plug of silica gel. The plug was eluted with diethyl ether and the filtrate was evaporated to afford 82.84 g (53%) of a light yellow oil that was shown by ^1H NMR to be a 3:1 mixture of the desired product and the isomeric alcohol at the 2-position of the thiophene. The mixture was used in the next step. 3-isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.29 (dd, 1H), 7.18 (d, 1H), 7.09 (d, 1H), 4.96 (m, 1H), 1.52 (d, 3H). 2-isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.22 (d, 1H), 6.96 (m, 1H), 6.92 (d, 1H), 5.23 (m, 1H), 1.57 (d, 3H).

[00200] 3-Acetylthiophene. The mixture of alcohols from the previous procedure was dissolved in 700 mL of toluene. Manganese oxide (131.82 g, excess) was added and the mixture was stirred at reflux overnight. The mixture was cooled, filtered, and evaporated in vacuo. The oil was dissolved in CH_2Cl_2 and filtered over a plug of silica gel. The plug was eluted with CH_2Cl_2 and the filtrate was evaporated in vacuo to afford the product as a yellow solid. The

product was a 3:1 mixture of the 3-acetyl and 2-acetylthiophene. 3-isomer: ^1H NMR (500 MHz, CDCl_3) δ 8.05 (dd, 1H), 7.53 (d, 1H), 7.31 (dd, 1H), 2.52 (s, 3H). 2-isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, 1H), 7.51 (d, 1H), 7.10 (d, 1H).

[00201] 3-Dimethylamino-1-thiophen-3-yl-propenone. The crude 3-acetylthiophene (42.81 g, 339 mmol) was mixed with 250 mL of dimethylformamide dimethyl acetal and heated to reflux overnight. The red solution was evaporated in vacuo. The resulting oil was dissolved in CH_2Cl_2 and washed with water. The organic solution was dried (MgSO_4), and evaporated in vacuo to afford 61.04 g (99%) of a light yellow oil that crystallized upon standing. ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, 1H), 7.74 (d, 1H), 7.52 (d, 1H), 7.25 (dd, 1H), 5.56 (d, 1H), 3.05 (br s, 3H), 2.91 (br s, 3H).

[00202] 4-Thiophen-3-yl-pyrimidine. 3-Dimethylamino-1-thiophen-3-yl-propenone (61.04 g, 337 mmol) was dissolved in 500 mL of DMF. Formamidinium hydrochloride (44.65 g, 555 mmol) was added along with 62.3 g (451 mmol) of K_2CO_3 . The mixture was heated to 80°C overnight. The mixture was poured into water and extracted with diethyl ether. The extract was dried (MgSO_4) and evaporated in vacuo to afford a brown solid. The solid was dissolved in CH_2Cl_2 and filtered over a plug of silica gel. The plug was eluted with CH_2Cl_2 and the filtrate was evaporated in vacuo to afford 44.7 g (82%) of 4-thiophen-3-yl-pyrimidine. ^1H NMR (500 MHz, CDCl_3) δ 9.18 (s, 1H), 8.70 (d, 1H), 8.13 (d, 1H), 7.69 (d, 1H), 7.53 (d, 1H), 7.43 (dd, 1H).

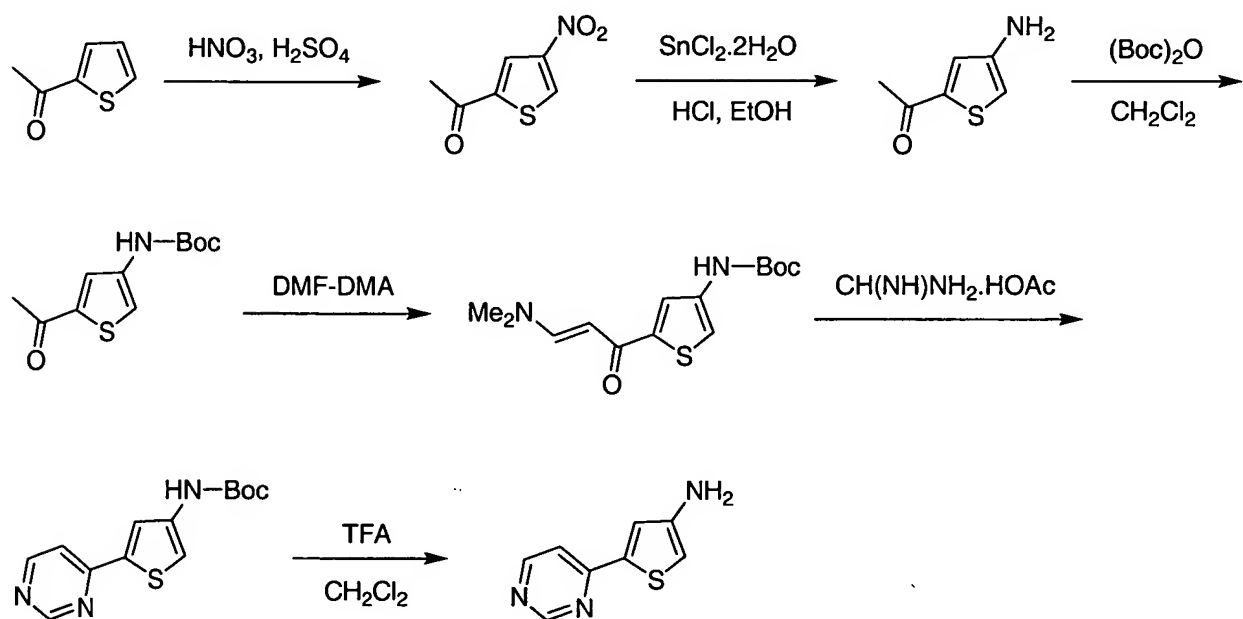
[00203] 4-(5-Nitro-thiophen-3-yl)-pyrimidine. 4-Thiophen-3-yl-pyrimidine (640 mg, 3.8 mmol) was dissolved in 10 mL of 98% sulfuric acid forming a red solution. The mixture was cooled to 0°C and 390 mg (3.86 mmol) of KNO_3 was added. The mixture was stirred for 10 minutes at 0°C and then one hour at room temperature. The mixture was poured into water and extracted numerous times with CH_2Cl_2 . The extract was dried and filtered over a plug of silica gel. The plug was eluted with CH_2Cl_2 and the filtrate was evaporated to afford 4-(5-nitro-thiophen-3-yl)-pyrimidine as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 9.22 (s, 1H), 8.81 (d, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 7.57 (d, 1H).

[00204] 4-Pyrimidin-4-yl-thiophen-2-ylamine hydrochloride. To a solution of 4-(5-nitro-thiophen-3-yl)-pyrimidine (0.20 g, 0.97 mmol) in 4 mL of 3:1 EtOAc – MeOH was added 50 mg of 10% palladium on carbon. The reaction was stirred at ambient temperature under 1 atmosphere of hydrogen gas for 4 hours, until no starting material remained by tlc analysis. The catalyst was filtered and washed with EtOAc and the filtrate was cooled to 0°C . The volume of

the filtrate volume was doubled with Et₂O, and then to the solution was added a solution of 4N HCl in dioxane (500 μ L, 2 mmol). A light yellow solid precipitated immediately, which was stirred for approximately 5 minutes at 0°C, and then filtered. The solids were washed with copious amounts of Et₂O with care taken not to expose the compound to air, and quickly transferred to high vacuum for drying. The solid was dried *in vacuo* to give 160 mg (77%) of 4-pyrimidin-4-yl-thiophen-2-ylamine hydrochloride as a pale yellow solid.

¹H NMR (500 MHz, DMSO-d₆) δ 9.17 (t, 1H, J=1.92Hz), 8.82-8.79 (m, 1H), 8.10 (s, 1H), 7.94-7.90 (m, 1H), 7.3 (bs, 2H). FIA/MS [M+H]⁺ = 308.

[00205] Preparation of 5-Pyrimidin-4-yl-thiophen-3-ylamine



Scheme 15

[00206] 2-Acetyl-4-nitrothiophene: Concentrated sulfuric acid (42.4 g, 0.44mol) was cooled to -10 °C and 2-acetylthiophene (20.2 g, 0.16mol) slowly added over 2 hours. Then a cold (-10 °C) mixture of 90% nitric acid (37.8 g, 0.60 mol) and concentrated sulfuric acid (28.1 g, 0.28 mol) was slowly added over 2 hours and the reaction mixture was stirred at -10 °C for another hour. The reaction mixture was slowly poured onto 300 g ice and the product precipitated out.

The crude 2-acetyl-4-nitrothiophene was washed with ether and filtered to afford 8.5g pure product. ^1H NMR (500 MHz, CDCl_3) δ 2.6 (s, 3H), 8.14 (d, 1H), 8.5 (d, 1H).

[00207] 2-Acetyl-4-aminothiophene: To an ethanol suspension of 0.524 g (0.003 mol) 2-acetyl-4-nitrothiophene and 2.1 g (0.009 mol) tin(II) chloride dihydrate was added 3 mL 6N HCl (0.018mol). The reaction mixture was stirred at 70 $^\circ\text{C}$ for 1 hour, then cooled to room temperature. The reaction mixture was adjusted to pH10 by addition of 6N NaOH, and the product was extracted into ethyl acetate. The product was purified by silica gel chromatography to afford 0.20 g 2-acetyl-4-aminothiophene (47%). ^1H NMR (500 MHz, CDCl_3) δ 2.52 (s, 3H), 6.5 (d, 1H), 7.23 (d, 1H).

[00208] 2-Acetyl-4-(t-butoxycarbonylamino)-thiophene: A solution of 2-acetyl-4-aminothiophene (1.2 g, 8.5 mmol) and di-tert-butyl dicarbonate (2.78 g, 12.7 mmol) in dichloromethane was stirred at room temperature over night. The solvent was removed by rotary evaporation and the product was purified by silica gel chromatography to afford 2-acetyl-4-(t-butoxycarbonylamino)-thiophene (1.48 g, 72%). ^1H NMR (500 MHz, CDCl_3) δ 1.5 (s, 9H), 2.5 (s, 3H), 6.66 (s, 1H), 7.36 (s, 1H), 7.65 (s, 1H).

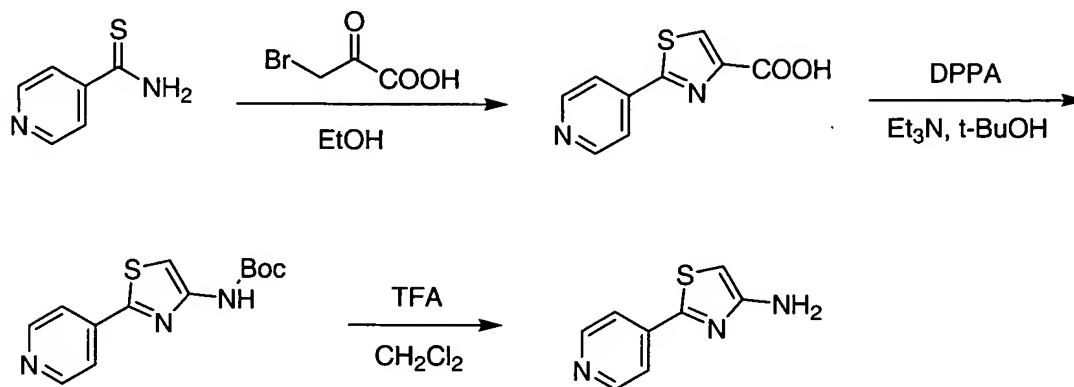
[00209] 2-(3-Dimethylaminopropenoyl)-4-(t-butoxycarbonylamino)-thiophene: A mixture of 2-acetyl-4-(t-butoxycarbonylamino)-thiophene (0.15 g, 0.622 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.296 g, 2.49mmol) was stirred at 75 $^\circ\text{C}$ for 24 h. The reaction mixture was rotary evaporated. ^1H NMR of the crude product indicated 90% product and 10% starting material. ^1H NMR (500 MHz, CDCl_3) δ 1.45 (s, 9H), 2.85 (s, 3H), 3.05 (s, 3H), 5.47 (d, 1H), 6.58 (s, 1H), 7.47 (s, 1H), 7.7 (d, 1H).

[00210] N-t-Butoxycarbonyl-5-pyrimidin-4-yl-thiophen-3-ylamine: 2-(3-Dimethylaminopropenoyl)-4-(t-butoxycarbonylamino)-thiophene (0.184 g, 0.622mmol) and formamidine acetate (0.388 g, 3.73 mmol) were heated at 115 $^\circ\text{C}$ for 6 h. The mixture was cooled to room temperature and ethyl acetate and brine added. The organic phase was dried with MgSO_4 and the product was purified by silica gel chromatography to afford N-t-butoxycarbonyl-5-pyrimidin-4-yl-thiophen-3-ylamine (0.1 g, 58%) ^1H NMR (500 MHz, CDCl_3) δ 1.48 (s, 9H), 6.68 (s, 1H), 7.21 (s, 1H), 7.45 (dd, 1H), 7.7 (s, 1H), 8.58 (d, 1H), 9.04 (d, 1H).

[00211] 5-Pyrimidin-4-yl-thiophen-3-ylamine: To a solution of N-t-butoxycarbonyl-5-pyrimidin-4-yl-thiophen-3-ylamine (0.1 g, 0.36mmol) in methylene chloride was added 0.5 mL TFA. The reaction mixture was stirred at room temperature for 3 h, then rotary evaporated. The

product was purified by silica gel chromatography to afford 5-pyrimidin-4-yl-thiophen-3-ylamine (60 mg, 93%). ¹H NMR (500 MHz, CDCl₃) δ 6.95 (s, 1H), 7.56 (s, 2H), 8.69 (s, 1H), 9.10 (s, 1H).

[00212] Preparation of 2-(Pyrid-4-yl)-4-amino-thiazole



Scheme 16

[00213] 2-(Pyrid-4-yl)-thiazole-4-carboxylic acid

[00214] Thioisonicotinamide (22.06 g, 0.16 mol) was suspended in reagent alcohol (280 mL) and warmed to 40 °C. Bromopyruvic acid (28.3 g, 0.16 mol) was dissolved in reagent alcohol (100 mL) and added via addition funnel. The reaction was refluxed for 2.5 h, then cooled to 4°C. The precipitate was filtered, washed with reagent alcohol and dried. The product was suspended in reagent alcohol (100 mL) and aqueous 2 N NaOH (80 mL) added. After stirring for 1 h the mixture was diluted with water (500 mL) and extracted with EtOAc (2 x 100 mL). The aqueous solution was acidified with 20% aqueous citric acid solution (500 mL) and the resulting precipitate was filtered, washed with water and dried. Yield 15.1 g. MS: [M+H] = 207; ¹H NMR (d₆-DMSO) 8.77 (2H, d), 8.67 (1H, s), 7.96 (2H, d), 1.50 (9H, s).

[00215] 2-(Pyrid-4-yl)-4-(t-butoxycarbonylamino)-thiazole

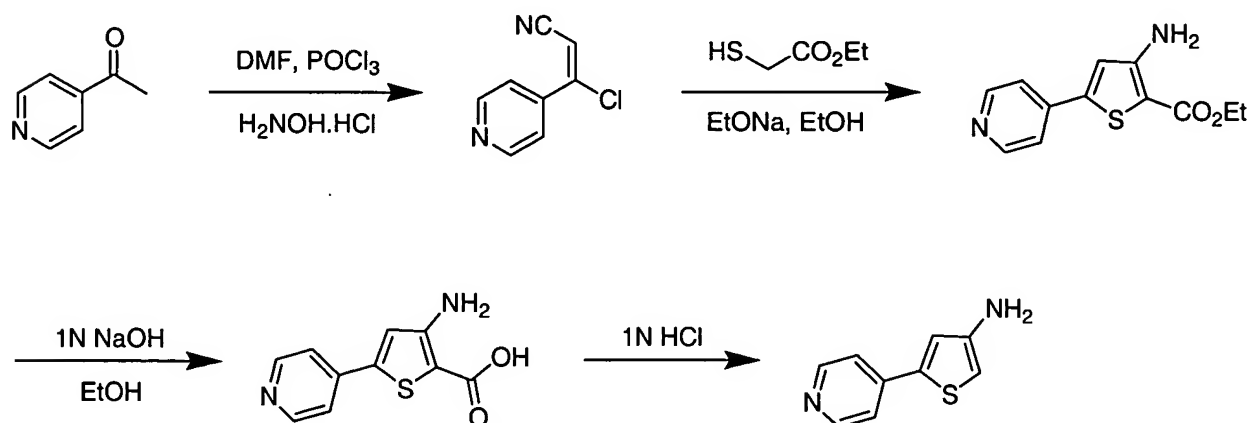
[00216] 2-(Pyrid-4-yl)-thiazole-4-carboxylic acid (16.96 g, 82 mmol) was suspended in t-butanol (250 mL) at 30 °C. Triethylamine (18 mL, 129 mmol) was added, followed by dropwise addition of diphenylphosphoryl azide (23.5 mL, 109 mmol). The solution was brought to reflux for 5 h, then allowed to cool. Solvent was partially removed by rotary evaporation, whereupon a

gelatinous mass formed. Ethyl acetate (300 mL) was added to give a clear, brown solution. Upon standing a solid precipitated, which was filtered, washed with EtOAc and dried. The filtrate was diluted to 1000 mL total volume with EtOAc and washed with water, saturated aqueous NaHCO_3 (x2), water, 5% aqueous citric acid (x2), water and brine. The solution was dried over Na_2SO_4 and evaporated to dryness. The solid was combined with that isolated previously and recrystallized from hot methanol. Yield 11.9 g. MS: $[\text{M}+\text{H}] = 278.1$; ^1H NMR (d_6 -DMSO) 10.45 (1H, br s), 8.72 (2H, d), 7.83 (2H, d), 7.49 (1H, s), 1.50 (9H, s).

[00217] 2-(Pyrid-4-yl)-4-amino-thiazole

[00218] 2-(Pyrid-4-yl)-4-(t-butoxycarbonylamino)-thiazole (12.49 g, 45.0 mmol) was suspended in methylene chloride (50 mL) and trifluoroacetic acid (60 mL) added. The solution was stirred at room temperature for 2 h, then evaporated to dryness. Methylene chloride (80 mL) was added and evaporated (x3). The product was triturated under anhydrous diethyl ether, filtered, washed with ether and dried. Yield 12.33 g. MS: $[\text{M}+\text{H}] = 178.1$; ^1H NMR (d_6 -DMSO) 8.75 (2H, d), 8.01 (2H, d), 6.35 (1H, s).

[00219] Preparation of 5-Pyridin-4-yl-thiophen-3-ylamine



Scheme 17

[00220] 3-Chloro-3-pyridin-4-yl-acrylonitrile: To DMF (29.2 g, 0.4 mol) was added phosphorus oxychloride (30.66 g, 0.2 mol) dropwise at $0 - 6^\circ\text{C}$ over 1.5 hours, then to this mixture was added 4-acetylpyridine (12.1 g, 0.1 mol) room temperature over 3.5 hours, the

internal temperature was below 60 °C, then to the reaction mixture was added hydroxylamine hydrochloride suspended in DMF over 4 hours (the reaction is extremely exothermic), then the reaction mixture was stirred at 80 °C for 4 hours. The reaction mixture was neutralized with saturated NaHCO₃ solution, the product was extracted into ethyl acetate, the organic solvent was removed, the product was purified by silica gel chromatography to afford 3-chloro-3-pyridin-4-yl-acrylonitrile (5.0 g, 30%). ¹H NMR (500 MHz, DMSO-d₆) δ 7.25 (s, 1H), 7.8 (d, 2H), 8.8 (d, 2H).

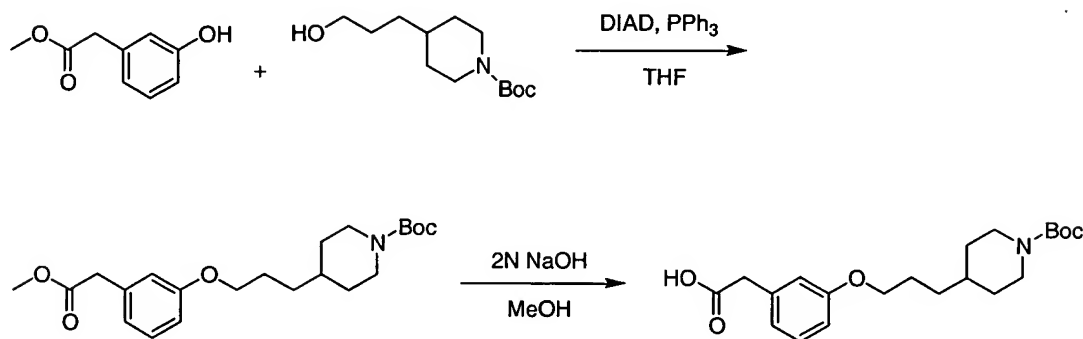
[00221] 3-Amino-5-pyridin-4-yl-thiophene-2-carboxylic acid ethyl ester: To a solution containing 3-chloro-3-pyridin-4-yl-acrylonitrile (8.3 g, 0.0504 mol) and ethyl 2-mercaptoacetate (7.27 g, 0.0605 mol) in ethanol was added sodium ethoxide (8.23 g, 0.121 mol). The reaction mixture was refluxed for 20 hours, ethyl acetate and brine added, and the organic phase was dried with MgSO₄. The solvent was removed under reduced pressure, the product was purified by crystallization from methylene chloride and hexanes, (10.0 g, 80%). ¹H NMR (500 MHz, DMSO-d₆) δ 1.3 (t, 3H), 4.23 (q, 2H), 6.63 (s, 1H), 7.60 (d, 2H), 8.60 (d, 2H).

[00222] 3-Amino-5-pyridin-4-yl-thiophene-2-carboxylic acid: 3-Amino-5-pyridin-4-yl-thiophene-2-carboxylic acid ethyl ester (6.0 g, 0.0242 mol) was dissolved in hot ethanol (20 mL), and to the solution was added 1N NaOH (24 mL). The reaction mixture was heated at 85 °C for 6 hours, then cooled to room temperature. The precipitated solid was filtered, washed with water and dried (4.6g, 86%). ¹H NMR (500 MHz, DMSO-d₆) δ 5.96 (s, br, 2H), 7.09 (s, 1H), 7.48 (d, 2H), 8.52 (d, 2H).

[00223] 5-Pyridin-4-yl-thiophen-3-ylamine: To 3-Amino-5-pyridin-4-yl-thiophene-2-carboxylic acid (4.6 g, 0.0209 mol) was added 1N HCl (50 mL) and the suspension was heated at 90 °C. The solid went into solution and after 30 min no more gas was formed. The reaction mixture was cooled to room temperature and neutralized by addition of 6N sodium hydroxide. The solid precipitate was filtered, washed and dried to afford 5-Pyridin-4-yl-thiophen-3-ylamine (2.5g, 67%). ¹H NMR (500 MHz, DMSO-d₆) δ 4.99 (s, br, 2H), 6.17 (s, 1H), 7.18 (s, 1H), 7.47 (d, 2H), 8.5 (d, 2H).

[00224] The synthesis of certain exemplary acids (for reaction with the amines described generally above) is described below. It will be appreciated that a variety of acids can be prepared according to the general methods described below.

[00225] Preparation of 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid



Scheme 18

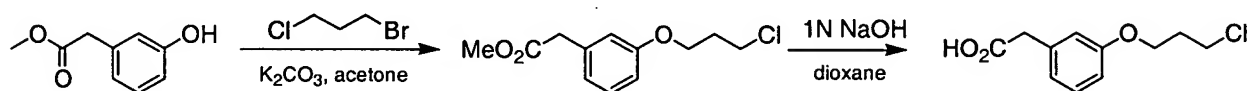
[00226] Methyl 3-hydroxyphenylacetate: 3-Hydroxyphenylacetic acid (75.3 g, 0.5 mol) was dissolved in methanol (900 mL). Concentrated sulfuric acid (2 mL) was added and the mixture refluxed for 5 hours. The solvent was evaporated and the residue dissolved in ethyl acetate (1000 mL) and washed with water (2 x 600 mL) and brine, and dried (MgSO₄). Solvent was evaporated to afford methyl 3-hydroxyphenylacetate as an oil (82 g, quantitative yield). ¹H NMR (500 MHz, CDCl₃) δ 7.2 (1H, t), 6.9 – 6.75 (3H, m), 5.5 (1H, br), 3.75 (3H, s), 3.63 (2H, s).

[00227] Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate: To THF solution of 0.409 g (2.4 mmol) methyl 3-hydroxyphenylacetate, 0.50 g (20.5 mmol) N-Boc-piperidin-4-yl-propanol and 0.645 g (24.6 mmol) triphenylphosphine was added diisopropyl azodicarboxylate at 0 °C slowly, then the ice bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was removed by rotary evaporation, the residue was dissolved in 2 mL methylene chloride and was loaded on a silica gel column and, the product eluted with 80% hexane and 20% ethyl acetate. Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 62%) was obtained. ¹H NMR (500 MHz, CDCl₃) δ 1.1 (m, 2H), 1.4 (m, 2H), 1.46 (s, 9H), 1.66 (d, 2H), 1.78 (m, 2H), 2.67 (t, 2H), 3.58 (s, 2H), 3.68 (s, 3H), 4.05 (m, 2H), 6.75 (m, 3H), 7.18 (dd, 1H).

[00228] 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid: Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 1.3 mmol) was dissolved in methanol, and 2N NaOH (3 mL) added. The reaction was stirred at 60 °C for 2h, then the solution was adjusted to pH 6.5, the product was extracted into ethyl acetate and the organic phase was dried by MgSO₄.

Removal of solvent revealed 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid (0.30 g). ¹H NMR (500 MHz, CDCl₃) δ 1.02 (m, 2H), 1.25 (m, 2H), 1.55 (m, 2H), 1.65 (m, 2H), 2.57 (m, 2H), 3.33 (m, 1H), 3.75 (s, 2H), 3.95 (m, 2H), 6.63 (m, 3H), 6.98 (m, 1H).

[00229] Preparation of 3-(3-chloro-propoxy)-phenylacetic acid

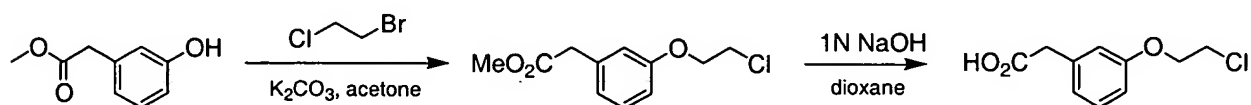


Scheme 19

[00230] Methyl 3-(3-chloro-propoxy)-phenylacetate: Methyl 3-hydroxyphenylacetate (87 g, 0.52 mol) was dissolved in acetone (500 mL). 1-Bromo-3-chloropropane (55 mL, 0.56 mol) was added, followed by potassium carbonate (73 g, 0.53 mol) and acetone (100 mL). The reaction was heated to reflux. After 24 hours, more 1-bromo-3-chloropropane (5 mL, 50 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was purified by passage over a short column of silica gel (650 g: 135 mm diameter column) eluted with hexane, and 30% ethyl acetate in hexane, to afford methyl 3-(3-chloro-propoxy)-phenylacetate (120g, 95%) as an oil. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (1H, dd), 6.93 – 6.85 (3H, m), 4.16 (2H, t), 3.79 (2H, t), 3.73 (3H, s), 3.62 (2H, s), 2.28 (2H, m).

[00231] 3-(3-Chloro-propoxy)-phenylacetic acid: Methyl 3-(3-chloro-propoxy)-phenylacetate (12.7 g, 52.3 mmol) was dissolved in dioxane (25 mL) and 1N NaOH (53 mL) was added. The mixture was stirred at room temperature for 45 minutes then acidified by addition of 1N hydrochloric acid (60 mL). A white precipitate formed which was filtered, washed with 1N HCl, water and dried. 3-(3-Chloro-propoxy)-phenylacetic acid (11.7 g, 98 %). ¹H NMR (500 MHz, CDCl₃) δ 7.25 (1H, dd), 6.93 – 6.85 (3H, m), 4.11 (2H, t), 3.79 (2H, t), 3.70 (2H, s), 2.25 (2H, m).

[00232] Preparation of 3-(2-chloro-ethoxy)-phenylacetic acid



Scheme 20

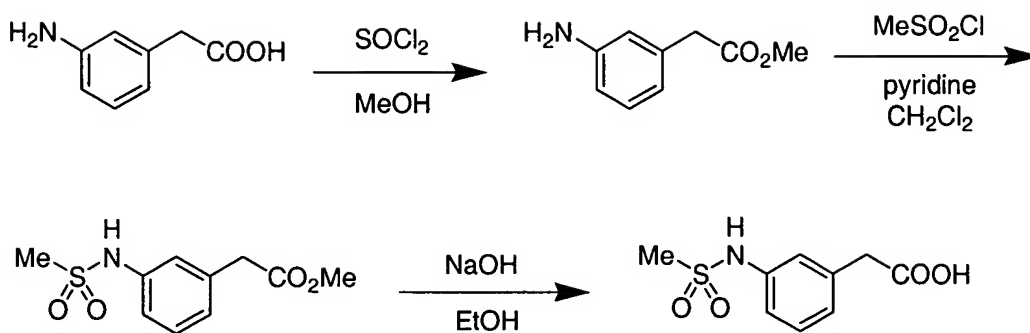
[00233] Methyl 3-(2-chloroethoxy)-phenylacetate: Methyl 3-hydroxyphenylacetate (10.8 g, 65 mmol) was dissolved in acetone (120 mL). 1-Bromo-2-chloroethane (5.5 mL, 66 mmol) was added, followed by potassium carbonate (10.1 g, 73.6 mmol). The reaction was heated to reflux. After 24 hours, more 1-bromo-2-chloroethane (11 mL, 132 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was purified by passage over a short column of silica gel eluted with hexane, and 30% ethyl acetate in hexane, to afford methyl 3-(3-chloroethoxy)-phenylacetate as an oil.

[00234] 3-(2-Chloroethoxy)-phenylacetic acid: Methyl 3-(2-chloro-ethoxy)-phenylacetate (7.0 g, 32.9 mmol) was dissolved in methanol (40 mL) and 6N NaOH (5.5 mL) was added. The mixture was stirred at room temperature overnight then acidified by addition of 6N hydrochloric acid (5.5 mL). A white precipitate formed which was filtered, washed with 1N HCl, water and dried. 3-(3-Chloroethoxy)-phenylacetic acid (6.5 g, 99 %). ¹H NMR (500 MHz, CDCl₃) δ 3.55 (s, 2H), 3.75 (t, 2H), 4.15 (t, 2H), 6.78 (dd, 1H), 6.80 (d, 1H), 6.84 (dd, 1H), 7.16 (dd, 1H).

[00235] Preparation of 3-Ethoxyphenylacetic acid

[00236] Methyl 3-ethoxyphenylacetate: Methyl 3-hydroxyphenylacetate (6.4 g, 38.5 mmol) was dissolved in acetone (50 mL). Ethyl bromide (3.5 mL, 46.9 mmol) was added, followed by potassium carbonate (6.37 g, 46 mmol). The reaction was heated to reflux. After 24 hours, more ethyl bromide (3.55 mL, 46.9 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was dissolved in ethyl acetate and the solution washed with saturated sodium bicarbonate (2 x 50 mL) and brine, and dried (MgSO₄). Removal of solvent revealed methyl 3-ethoxyphenylacetate as an oil that crystallized upon standing. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (1H, dd), 6.87 (3H, m), 4.08 (2H, q), 3.73 (3H, s), 3.65 (2H, s), 1.45 (3H, t).

[00237] 3-Ethoxyphenylacetic acid: Methyl 3-ethoxyphenylacetate (7.5 g, 38.6 mmol) was dissolved in ethanol (15 mL) and 1N NaOH (40 mL) was added. The mixture was stirred at room temperature for 30 minutes then acidified by addition of 1N hydrochloric acid (45 mL). A white precipitate formed which was filtered, washed with 1N HCl, water and dried. 3-Ethoxyphenylacetic acid (6.4 g, 92 %). ¹H NMR (500 MHz, CDCl₃) δ 7.20 (1H, dd), 6.8 (3H, m), 4.0 (2H, q), 3.6 (2H, s), 1.4 (3H, t).



Scheme 21

[00238] Preparation of 3-(Methanesulfonyl)phenylacetic acid

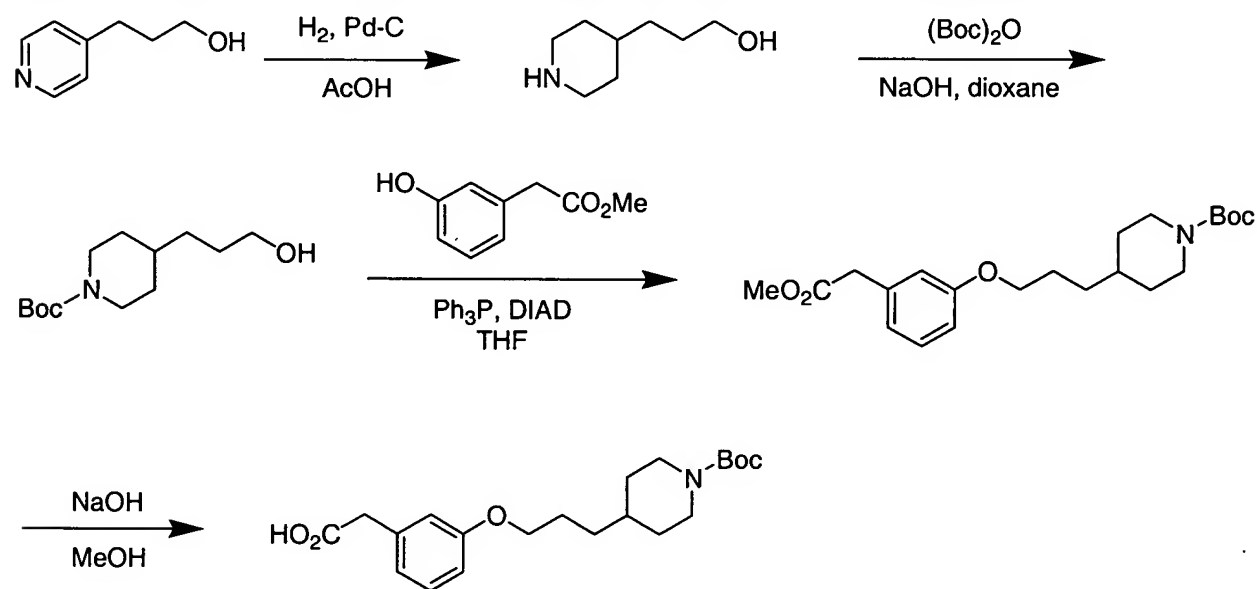
[00239] Methyl 3-aminophenylacetate: 3-Aminophenylacetic acid (15.5 g, 0.10 mol) was suspended in methanol (150 mL) and cooled to 0 °C. Thionyl chloride (11.2 mL, 0.15 mol) was added dropwise under stirring. A clear orange solution was obtained, which was stirred for 4 hours, then evaporated. The solid residue was partitioned between ethyl acetate (150 mL) and saturated sodium bicarbonate (150 mL) and the organic phase washed with saturated sodium bicarbonate (100 mL), and brine and dried (Na₂SO₄). Methyl 3-aminophenylacetate was isolated as a brown oil. (14.1g, 83%). ¹H NMR (500 MHz, CDCl₃) δ 7.12 (1H, dd), 6.7 – 6.6 (3H, m), 3.71 (3H, s), 3.55 (2H, s).

[00240] Methyl 3-(methanesulfonyl)phenylacetate: Methyl 3-aminophenylacetate (2.26 g, 13.7 mmol) was dissolved in dry methylene chloride (20 mL) and cooled to 0 °C. Pyridine (2.2 mL, 27.2 mmol) was added followed by dropwise addition of methanesulfonyl chloride (1.3 mL, 16.8 mmol). The mixture was stirred at 0 °C for 1 hour and at room temperature for 3 hours, then poured into 100 mL of saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate (100 mL), 1N HCl (2 x 100 mL) and brine. Dried over MgSO₄. Solvent was evaporated to reveal methyl 3-(methanesulfonyl)phenylacetate. (3.36 g, 100%). ¹H NMR (500 MHz, CDCl₃) δ 7.32 (1H, dd), 7.2 – 7.1 (3H, m), 6.57 (1H, s), 3.72 (3H, s), 3.64 (2H, s), 3.02 (3H, s).

[00241] 3-(Methanesulfonyl)phenylacetic acid: Methyl 3-(methanesulfonyl)phenylacetate (3.36 g, 13.8 mmol) was dissolved in ethanol (16 mL) and 1N NaOH (30 mL) added. The reaction was stirred for 1 hour, then 1N HCl (50 mL) and water (50 mL) were added. The

product was extracted into ethyl acetate (3 x 50 mL) and the combined extracts were washed with water and brine and dried (MgSO₄). Removal of solvent afforded 3-(methanesulfonyl)phenylacetic acid (2.90 g, 92%). ¹H NMR (500 MHz, DMSO-d₆) δ 12.32 (1H, br), 9.69 (1H, br), 7.26 (1H, dd), 7.10 (2H, m), 7.00 (1H, d), 6.57 (1H, s), 3.54 (2H, s), 2.97 (3H, s).

[00242] Preparation of 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid



Scheme 22

[00243] 3-Piperidin-4-yl-propan-1-ol: 4-Pyridinepropanol (10.0 g, 73 mmol) was dissolved in glacial acetic acid (50 mL). 10% Palladium on carbon (1.1 g) was added and the mixture hydrogenated under 50 psi hydrogen gas for 6 days. The mixture was filtered through Celite and the solvent removed by rotary evaporation. The crude product 3-piperidin-4-yl-propan-1-ol (acetic acid salt) was used as obtained. ¹H NMR (500 MHz, CDCl₃) δ 6.3 (br), 3.65 (2H, t), 3.36 (2H, m), 2.79 (2H, dt), 2.01 (3H, s), 1.85 (2H, m), 1.7 – 1.3 (7H, m).

[00244] 3-(N-Boc-Piperidin-4-yl)-propan-1-ol: The crude 3-piperidin-4-yl-propan-1-ol (73 mmol) was dissolved in dioxane (100 mL) and 3N NaOH (25 mL) was added to give a pH9 solution. Di-tert-butyl dicarbonate (16.0 g, 73 mmol) in dioxane (35 mL) was added dropwise, with simultaneous addition of 3N NaOH to maintain the solution at approximately pH9. After 2 hours no residual amine was visible by TLC (ninhydrin stain) and the reaction was diluted with

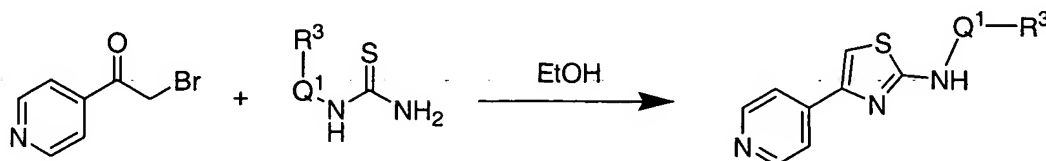
water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with water and brine and dried (MgSO₄). Removal of solvent afforded 20 g crude product which was purified by silica gel chromatography (200 g silica) in a sintered glass funnel (L.M. Harwood, Aldrichimica Acta, 1985, 18, 25) eluted with 500 mL each of hexane, 20%, 40%, 60% and 80% ethyl acetate in hexane. 3-(N-Boc-Piperidin-4-yl)-propan-1-ol was isolated as a clear, colorless oil (14.5 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 4.09 (2H, m), 3.66 (2H, t), 2.69 (2H, dt), 1.7-1.5 (4H, m), 1.47 (9H, s), 1.4 - 1.3 (5H, m), 1.12 (2H, m).

[00245] Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate: To a solution of methyl 3-hydroxyphenylacetate (0.409 g, 2.4 mmol), 3-(N-Boc-piperidin-4-yl)-propan-1-ol (0.50 g, 20.5 mmol) and triphenylphosphine (0.645, 24.6 mmol) in THF, was added diisopropyl azodicarboxylate at 0 °C slowly, then the ice bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in methylene chloride (2 mL) and loaded on a silica gel column. The product was eluted with 20% ethyl acetate in hexane, to afford methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 62%). ¹H NMR (500 MHz, CDCl₃) δ 1.1 (m, 2H), 1.4 (m, 2H), 1.46 (s, 9H), 1.66 (d, 2H), 1.78 (m, 2H), 2.67 (t, 2H), 3.58 (s, 2H), 3.68 (s, 3H), 4.05 (m, 2H), 6.75 (m, 3H), 7.18 (dd, 1H).

3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid: Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 1.3 mmol) was dissolved in methanol and 2N NaOH (3 mL) added. The reaction was stirred at 60 °C for 2 hours then the solution was adjusted to pH 6.5. The product was extracted into ethyl acetate, and the organic phase was dried by MgSO₄. The solvent was evaporated to afford 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid (0.30 g). ¹H NMR (500 MHz, CDCl₃) δ 1.02 (m, 2H), 1.25 (m, 2H), 1.55 (m, 2H), 1.65 (m, 2H), 2.57 (m, 2H), 3.33 (m, 1H), 3.75 (s, 2H), 3.95 (m, 2H), 6.63 (m, 3H), 6.98 (m, 1H).

[00246] PREPARATION OF EXEMPLARY COMPOUNDS

[00247] Preparation of 2-amino-4-(4-pyridyl)thiazoles

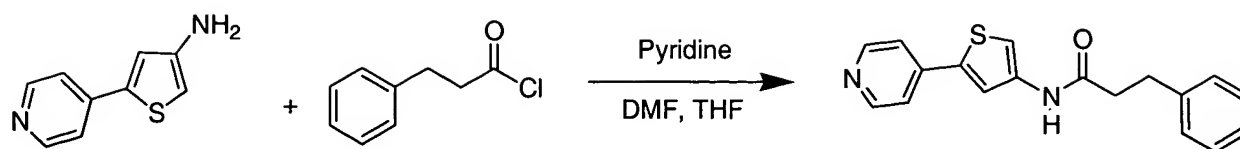


Scheme 23

[00248] 4-Pyridin-4-yl-thiazol-2-ylamine: To 4-(bromoacetyl)-pyridine hydrobromide (Can. J. Chem., 1970, 7, 1137) (97.5 g, 0.35 mol) and thiourea (26.5 g, 0.35 mol) was added ethanol (900 mL) and the mixture heated to reflux for 2 hours. After cooling to 4 °C the product was filtered, washed with ethanol and diethyl ether and dried under suction. The solid 4-pyridin-4-yl-thiazol-2-ylamine dihydrobromide (88.7 g) was dissolved in warm water (500 mL) and the desired 4-Pyridin-4-yl-thiazol-2-ylamine obtained as a light brown solid upon addition of 7% aqueous ammonium hydroxide (800 mL). 43.5 g, 71%. ¹H NMR (500 MHz, DMSO-d₆) δ 8.53 (2H, d), 7.71 (2H, d), 7.38 (1H, s), 7.16 (2H, br).

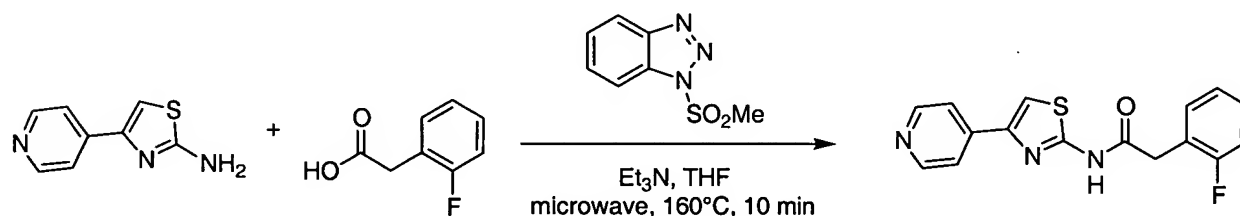
[00249] Methyl-(4-pyridin-4-yl-thiazol-2-yl)-amine: To 4-(bromoacetyl)-pyridine hydrobromide (Can. J. Chem., 1970, 7, 1137) (16.7 g, 59 mmol) and N-methylthiourea (5.4 g, 60 mmol) was added ethanol (160 mL) and the mixture heated to reflux for 1 hour. A thick solid formed. After cooling to 4 °C the product was filtered, washed with ethanol and diethyl ether and dried under suction. The solid methyl-4-pyridin-4-yl-thiazol-2-ylamine dihydrobromide (15 g) was stirred in 1N NaOH (100 mL) for 30 min then filtered, washed with 1N NaOH and water, and dried to afford methyl-4-pyridin-4-yl-thiazol-2-ylamine (7.6 g, 67%). [M+H]⁺ = 192. ¹H NMR (500 MHz, DMSO-d₆) δ 8.55 (2H, d), 7.76 (2H, d), 7.67 (1H, br), 7.42 (1H, s), 2.90 (3H, d).

[00250] Ethyl-(4-pyridin-4-yl-thiazol-2-yl)-amine: To 4-(bromoacetyl)-pyridine hydrobromide (Can. J. Chem., 1970, 7, 1137) (16.7 g, 59 mmol) and N-ethylthiourea (6.3 g, 61 mmol) was added ethanol (160 mL) and the mixture heated to reflux for 1 hour. A thick solid formed. After cooling to 4 °C the product was filtered, washed with ethanol and diethyl ether and dried under suction. The solid ethyl-4-pyridin-4-yl-thiazol-2-ylamine dihydrobromide (13.7 g) was stirred in 1N NaOH (100 mL) for 30 min then filtered, washed with 1N NaOH and water, and dried to afford ethyl-4-pyridin-4-yl-thiazol-2-ylamine (6.7 g, 56%). [M+H]⁺ = 206. ¹H NMR (500 MHz, DMSO-d₆) δ 8.56 (2H, d), 7.75 (3H, m), 7.40 (1H, s), 3.3 (2H, obscured), 1.20 (3H, t).



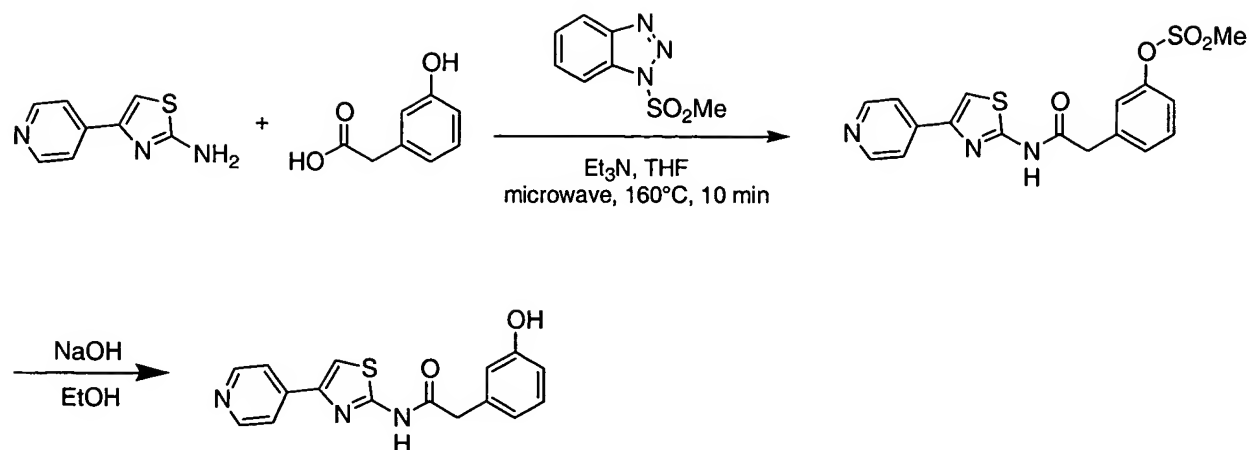
Scheme 24

[00251] 3-Phenyl-N-(5-pyridin-4-yl-thiophen-3-yl)-propionamide: A DMF/THF solution containing 5-pyridin-4-yl-thiophen-3-ylamine (60mg, 0.341 mmol), hydrocinnamyl chloride (76.8 mg, 0.411 mmol), and pyridine (32 mg, 0.411 mmol) was stirred at 70 °C for 3 hours, then the solvent was removed, the residue was dissolved in MeOH and purified by preparative HPLC. ¹H NMR (500 MHz, DMSO-d₆) δ 2.64 (t, 2H), 2.92(t, 2H), 7.17 (m, 1H), 7.28 (m, 4H), 7.8 (s, 1H), 7.85 (s, 1H), 7.93 (d, 2H), 8.73 (d, 2H), 10.52 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 2.30 min, [M+H]⁺ = 309, [M-H]⁻ = 307.



Scheme 25

[00252] 2-(2-Fluorophenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 4-(4-Pyridyl)-2-aminothiazole (329 mg, 1.86 mmol), 2-fluorophenylacetic acid (377 mg, 2.25 mmol) and N-(1-methanesulfonyl)benzotriazole (440 mg, 2.23 mmol) were placed in a microwave reaction vessel (Personal Chemistry, Uppsala, Sweden). THF (2 mL) was added followed by triethylamine (0.52 mL, 3.73 mmol) and the mixture heated in the sealed tube at 160 °C for 10 minutes. Upon cooling to room temperature the product 2-(2-fluorophenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide precipitated, was filtered, washed with acetonitrile and dried. (462 mg, 76%). ¹H NMR (500 MHz, DMSO-d₆) δ 12.68 (1H, s), 8.63 (2H, d), 8.00 (1H, s), 7.84 (2H, d), 7.43-7.17 (4H, m), 3.90 (2H, s). LC-MS Rt = 1.9 min, [M+H]⁺ = 314, [M-H]⁻ = 312.

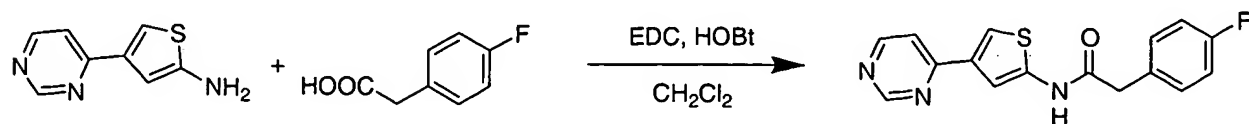


Scheme 26

[00253] Methanesulfonic acid 3-[(4-pyridin-4-yl-thiazol-2-ylcarbamoyl)-methyl]-phenyl ester: 4-(4-Pyridyl)-2-aminothiazole (317 mg, 1.79 mmol), 3-hydroxyphenylacetic acid (343 mg, 2.25 mmol) and N-(1-methanesulfonyl)benzotriazole (927 mg, 4.70 mmol) were placed in a microwave reaction vessel (Personal Chemistry, Uppsala, Sweden). THF (2 mL) was added followed by triethylamine (1.24 mL, 8.93 mmol) and the mixture heated in the sealed tube at 160 °C for 10 minutes. Upon cooling to room temperature the solvent was concentrated and ethanol added. The mixture was stored at -20 °C and then the precipitated product was filtered, washed with ethanol and dried. (910 mg, 65%). ¹H NMR (500 MHz, DMSO-d₆) δ 12.62 (1H, s), 8.63 (2H, d), 7.98 (1H, s), 7.84 (2H, d), 7.47 (1H, m), 7.36 (2H, m), 7.27 (1H, m), 3.89 (2H, s), 3.40 (3H, s). LC-MS Rt = 2.1 min, [M+H]⁺ = 390, [M-H]⁻ = 388.

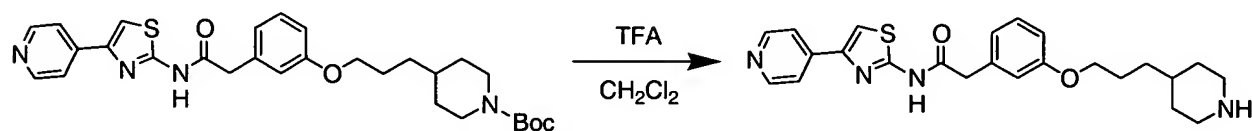
[00254] 2-(3-Hydroxyphenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: Methanesulfonic acid 3-[(4-pyridin-4-yl-thiazol-2-ylcarbamoyl)-methyl]-phenyl ester (400 mg) was suspended in ethanol (6 mL) and 1N NaOH (2 mL) added. The mixture was stirred at 50 °C. After 15 hours 2N NaOH (2mL) was added and the reaction stirred for a further 5 hours at 50 °C. 1N Hydrochloric acid was added to precipitate the product. ¹H NMR (500 MHz, DMSO-d₆) δ 12.7 (1H, s), 9.45 (1H, br s), 8.88 (2H, d), 8.35 (1H, s), 8.20 (2H, d), 7.21 (1H, t), 6.85 (2H, m), 6.70 (1H, d), 3.80 (2H, s). LC-MS Rt = 1.5 min, [M+H]⁺ = 312, [M-H]⁻ = 310.

[00255]



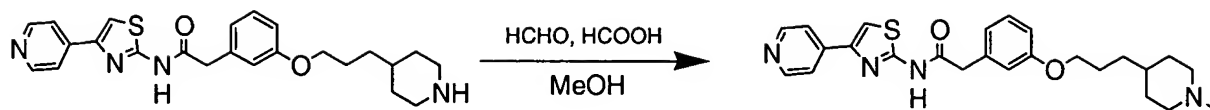
Scheme 27

[00256] 2-(4-Fluorophenyl)-N-(4-pyrimidin-4-yl-thiophen-2-yl)-acetamide: To a solution of 4-pyrimidin-4-yl-thiophen-2-ylamine (0.010g, 0.047mmol) in DCM (1mL) was added 1-ethyl-(dimethylaminopropyl)carbodiimide hydrochloride (0.025g, 0.13mmol), 1-hydroxybenzotriazole (0.015g, 0.11mmol), and 4-fluorophenylacetic acid (0.025g, 0.16mmol). The material was stirred for 5 minutes at RT, and then triethylamine (0.20mL, 1.43mmol) was added drop-wise over one minute. The reaction was stirred for one hour, then partitioned between EtOAc and water and the organic layer was dried with sodium sulfate. The solution was evaporated and stripped to a glassy residue which was purified by flash chromatography on silica gel by eluting with 50% EtOAc-hexane. The product 2-(4-fluorophenyl)-N-(4-pyrimidin-4-yl-thiophen-2-yl)-acetamide is obtained (6.4mg, 43%) as colorless glass. ¹H NMR (500 MHz, DMSO-d₆) δ 9.06 (s, 1H), 8.62 (d, 1H), 8.00 (s, 1H), 7.57 (d, 1H), 7.41 (d, 1H), 7.42-7.22 (m, 2H), 7.11-7.00 (m, 2H), 3.69 (s, 2H) LC-MS (10-90% CH₃CN in H₂O), Rt = 2.90min, [M+H]⁺ = 314, [M-H]⁻ = 312.1.



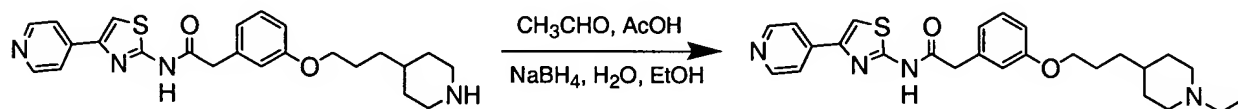
Scheme 28

[00257] 2-(3-(3-(Piperidin-4-yl)-propoxy)-phenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 2-(3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide was dissolved in methylene chloride and TFA added. After stirring for 4 hours at room temperature the solvents were evaporated and the residue purified by HPLC. ¹H NMR (500 MHz, CD₃OD) δ 1.4 (m, 2H), 1.5 (m, 2H), 1.67 (m, 1H), 1.81 (m, 2H), 1.95 (dd, 2H), 2.94 (t, 2H), 3.35 (dd, 2H), 3.78 (s, 2H), 4.0 (t, 2H), 6.83 (dd, 1H), 6.9 (dd, 1H), 6.92 (d, 1H), 7.24 (dd, 1H), 8.19 (s, 1H), 8.4 (d, 2H), 8.74 (d, 2H). LC-MS (5-45% CH₃CN in H₂O, Rt = 2.39 min, [M+H]⁺ = 437, [M-H]⁻ = 435.



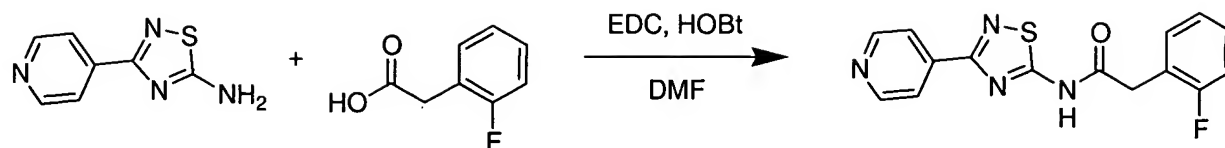
Scheme 29

[00258] 2-(3-(3-(N-Methyl-Piperidin-4-yl)-propoxy)-phenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 2-[3-(3-Piperidin-4-yl-propoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (1 equiv.), formaldehyde (30 equiv.) and formic acid (30 equiv.) in methanol solution were heated in a sealed tube at 80 °C for 48 hours. The reaction mixture was diluted with ethyl acetate and brine, and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation and the product was purified by HPLC. ¹H NMR (500 MHz, CD₃OD) δ 1.43 (m, 1H), 1.5 (m, 2H), 1.62(m, 1H), 1.82 (m 2H), 2.05 (d, 2H), 2.84 (s, 3H), 2.95 (t, 2H), 3.46 (d, 2H), 3.79 (s, 2H), 4.02 (t, 2H), 6.82 (d, 1H), 6.9 (d, 1H), 6.9 (s, 1H), 7.24 (dd, 1H), 8.05 (s, 1H), 8.24 (d, 2H), 8.68 (d, 2H). LC-MS (5-45% CH₃CN in H₂O, Rt = 2.68 min, [M+H]⁺ = 451, [M-H]⁻ = 449.



Scheme 30

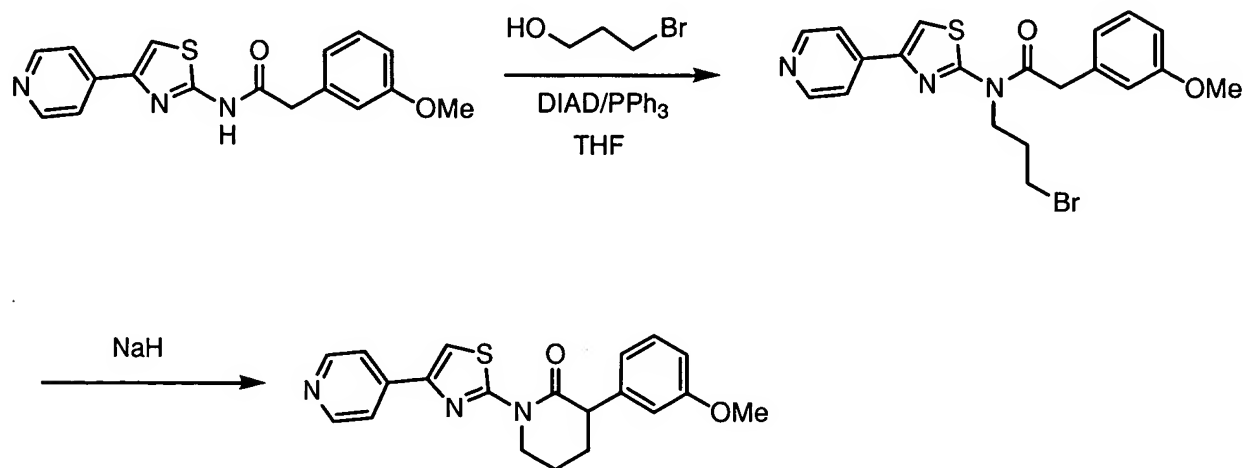
[00259] 2-(3-(3-(N-Ethyl-Piperidin-4-yl)-propoxy)-phenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 2-[3-(3-Piperidin-4-yl-propoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (1 equiv.), acetaldehyde (30 equiv.) and acetic acid (30 equiv.) in ethanol solution were treated with water (4 drops) and sodium borohydride. The reaction was stirred at room temperature for 5 minutes. The reaction mixture was diluted with ethyl acetate and brine, and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation and the product was purified by HPLC. ¹H NMR (500 MHz, CD₃OD) δ 8.75 (d, 2H), 8.43 (d, 2H), 8.23 (s, 1H), 7.23 (dd, 1H), 6.93 (d, 2H), 6.84 (d, 1H), 3.98 (q, 2H), 3.79 (s, 2H), 3.55 (d, 2H), 3.14 (q, 2H), 2.87 (t, 2H), 2.05 (d, 2H), 1.83 (m, 2H), 1.65 (m, 1H), 1.46 (m, 2H), 1.40 (d, 2H), 1.32 (t, 3H). LC-MS (5-45% CH₃CN in H₂O, Rt = 2.48 min, [M+H]⁺ = 465, [M-H]⁻ = 463.



Scheme 31

[00260] 2-(2-Fluorophenyl)-N-(3-pyridin-4-yl-[1,2,4]thiadiazol-5-yl)-acetamide: 2-Fluorophenylacetic acid (86 mg, 0.56 mmol), was dissolved in DMF (2mL). 1-Hydroxybenzotriazole (89 mg, 0.66 mmol) and 1-ethyl-(dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.6 mmol) were added and the mixture stirred at room temperature for 10 minutes. 3-Pyridin-4-yl-[1,2,4]thiadiazol-5-ylamine (100 mg, 0.56 mmol), was added and stirring continued for 4 hours. The DMF was evaporated and the residue washed with water. The crude product was then purified by preparative thin layer chromatography (5% methanol in methylene chloride), affording 5 mg of 2-(2-fluorophenyl)-N-(3-pyridin-4-yl-[1,2,4]thiadiazol-5-yl)-acetamide. ¹H NMR (500 MHz, CD₃OD) δ: 8.8 (m, 1H), 8.7 (m, 1H), 8.2 (m, 1H), 7.8 (m, 1H), 7.3 (m, 2H), 7.1 (m, 2H), 4.2 (s, 1H), 4.0 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 2.31 min, [M+H]⁺ = 315, [M-H]⁻ = 313.

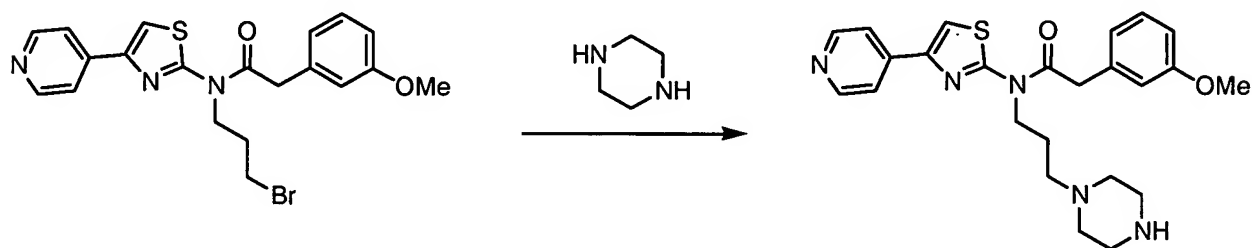
[00261]



Scheme 32

[00262] 3-(3-Methoxy-phenyl)-1-(4-pyridin-4-yl-thiazol-2-yl)-piperidin-2-one: 2-(3-Methoxy-phenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (prepared according to General

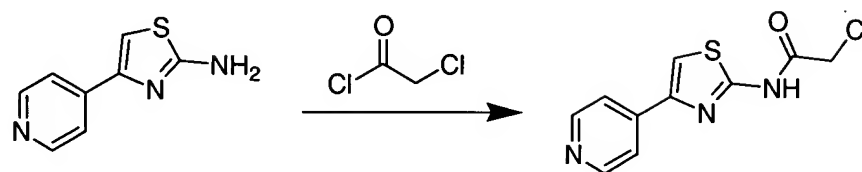
Method A from 4-(4-pyridyl)-2-aminothiazole and 3-methoxyphenylacetic acid: 1 mmol), triphenylphosphine (1.2 mmol), diisopropyl azodicarboxylate (1.2 mmol) and THF were stirred overnight at room temperature. The mixture was then cooled to 0 °C and NaH (1.2 mmol) added and reaction mixture was stirred at 0 °C for 30 minutes. MeOH was added to quench the reaction. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with H₂O and dried over Na₂SO₄. The product was purified by flash column chromatography on silica gel to afford 3-(3-methoxyphenyl)-1-(4-pyridin-4-yl-thiazol-2-yl)-piperidin-2-one in 60% yield. ¹H NMR (500 MHz, DMSO-d₆) δ 8.67 (d, 2H), 7.80 (d, 2H), 7.46 (s, 1H), 7.30 (m, 1H), 6.85 (m, 3H), 4.57 (m, 1H), 4.32 (m, 1H), 3.93 (m, 1H), 3.82 (s, 3H), 2.36 (m, 1H), 2.25 (m, 1H), 2.15 (m, 2H). LC-MS (10-90% CH₃CN in H₂O), Rt = 2.40 min, [M+H]⁺ = 366, [M-H]⁻ = 364.



Scheme 33

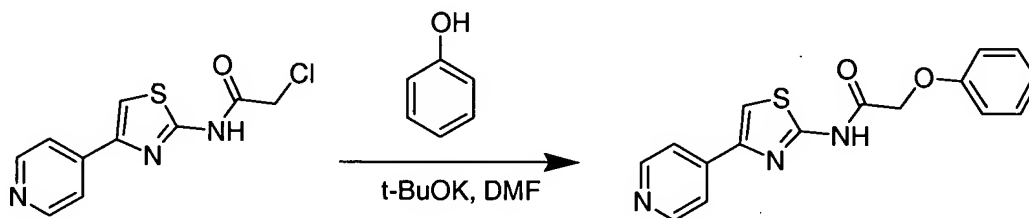
[00263] 2-(3-Methoxy-phenyl)-N-(3-piperazin-1-yl-propyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 2-(3-Methoxyphenyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (prepared according to General Method A from 4-(4-pyridyl)-2-aminothiazole and 3-methoxyphenylacetic acid: 1 mmol), triphenylphosphine (1.2 mmol), diisopropyl azodicarboxylate (1.2 mmol) and THF were stirred overnight at room temperature. Piperazine (3 mmol) was added and reaction mixture was heated to 60 °C for 1 hour. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with H₂O and dried over Na₂SO₄. The product was purified by flash column chromatography on silica gel to afford 2-(3-methoxyphenyl)-N-(3-piperazin-1-yl-propyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide 70 % yield. ¹H NMR (500 MHz, CD₃OD) δ 8.78 (d, 2H), 8.47 (d, 2H), 8.32 (s, 1H), 7.30 (m, 1H), 6.90 (m, 3H), 4.43 (t, 2H), 4.16 (s, 2H), 3.78 (s, 3H), 3.30 (m, 4H obscured), 2.87 (br, 4H), 2.85 (t, 2H), 2.06 (m, 2H). LC-MS (5-45% CH₃CN in H₂O, Rt = 1.80 min, [M+H]⁺ = 452, [M-H]⁻ = 450.

[00264] Preparation of N, O, and S-linked acetamides



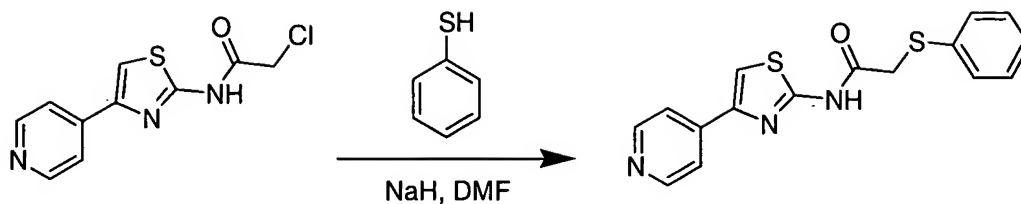
Scheme 34

[00265] 2-Chloro-N-(4-pyridin-4-ylthiazol-2-yl)-acetamide: A solution of 4-pyridin-4-ylthiazol-2-ylamine (3.64 g, 0.02 mol) and chloroacetyl chloride (3.39 g, 0.03 mol) in dioxane was refluxed overnight then cooled to room temperature. The solid precipitate was filtered, then the filtration cake was suspended in saturated KHCO₃, then filtered again. The filtration cake was washed with water dried in dessicator over P₂O₅. 2-Chloro-N-(4-pyridin-4-ylthiazol-2-yl)-acetamide (4.3 g, 85%). ¹H NMR (500 MHz, DMSO-d₆) δ 4.42 (s, 2H), 7.9 (d, 2H), 8.77 (d, 2H).



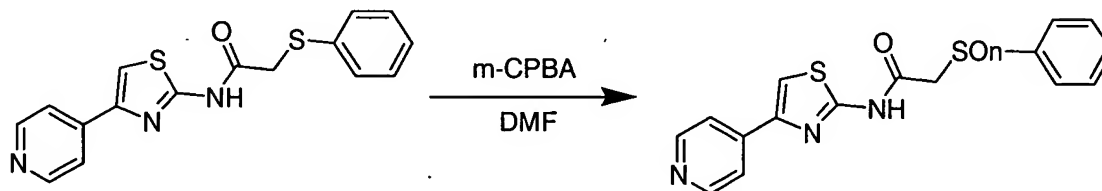
Scheme 35

[00266] 2-Phenoxy-N-(4-pyridin-4-ylthiazol-2-yl)-acetamide: 2-Chloro-N-(4-pyridin-4-ylthiazol-2-yl)-acetamide (1 mmol) was added to a stirred DMF solution (45 °C, 2h) containing phenol (3 mmol) and t-BuOK (3 mmol). The reaction mixture was stirred at 80°C for 8 h. To the reaction mixture was added ethyl acetate and brine, and the organic phase was dried with MgSO₄. The product was purified by HPLC. ¹H NMR (500 MHz, DMSO-d₆) δ 4.92(s, 2H), 7.0(m, 3H), 7.35(dd, 2H), 8.17(d, 2H), 8.33(s, 1H), 8.8(d, 2H), 12.7(s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 1.67 min, [M+H]⁺ = 312, [M-H]⁻ = 310.



Scheme 36

[00267] 2-Phenylsulfanyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: To a flask containing NaH (65%: 0.53 g, 1.32 mmol) was added a DMF solution of thiophenol (0.146 g, 1.32 mmol). The reaction mixture was stirred at room temperature until no more gas was released. To this was added 2-chloro-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (0.112 g, 0.4 mmol) in DMF and the reaction mixture was stirred at 60 °C for 5 hours. To the reaction mixture was added ethyl acetate and brine, and the organic phase was dried with MgSO₄. The solvent was removed, and the product was purified by silica gel chromatography. 2-Phenylsulfanyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (0.080g , 55%). ¹H NMR (500 MHz, DMSO-d₆) δ 4.0 (s, 2H), 7.24 (m, 1H), 7.35 (dd, 2H), 7.40 (d, 2H), 8.83 (d, 2H), 8.02 (s, 1H), 8.62 (d, 2H), 12.65 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 5.09 min, [M+H]⁺ = 328, [M-H]⁻ = 326.

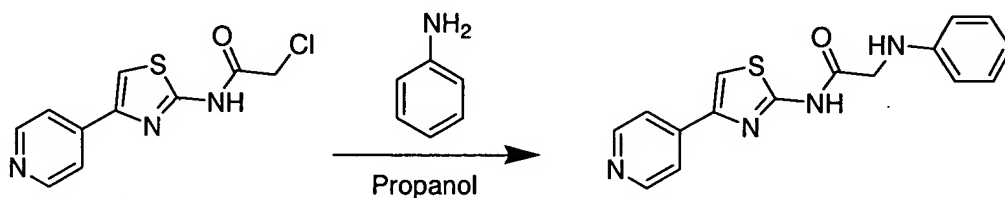


Scheme 37

[00268] 2-Benzenesulfonyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (Scheme 37: n = 2): To 2-phenyl-sulfanyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (0.08 g, 0.244 mmol) in DMF was added m-CPBA (77%: 0.081 g, 0.366 mmol), and the reaction mixture was stirred at 40 °C for 1 h, TLC indicated 2 new spots and no starting material. . To the reaction mixture was added ethyl acetate and brine, and the organic phase was dried with MgSO₄. 2-Benzenesulfonyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide was isolated following by preparative HPLC. ¹H NMR (500 MHz, DMSO-d₆) δ 4.7 (s, 2H), 7.68 (dd, 2H), 7.80 (dd, 1H), 7.94 (d, 2H), 8.15 (d, 2H),

8.35 (s, 1H), 8.82 (d, 2H), 12.82 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 3.77 min, [M+H]⁺ = 360, [M-H]⁻ = 358.

[00269] 2-Benzenesulfinyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (Scheme 37: n = 1): To 2-phenylsulfanyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (30 mg, 91.7 μmol) in DMF was added m-CPBA (77%: 20 g, 91.7 μmol), and the reaction mixture was stirred at 40 °C for 1h, then diluted with water. 2-Benzenesulfinyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide was isolated following by preparative HPLC (20 mg, 64%). ¹H NMR (500 MHz, DMSO-d₆) δ 4.07 (d, 1H), 4.29 (d, 1H), 7.60 (m, 3H), 7.75 (d, 1H), 8.20 (d, 2H), 8.41(s, 1H), 8.84 (d, 2H), 12.74 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 3.36 min, [M+H]⁺ = 344, [M-H]⁻ = 342.

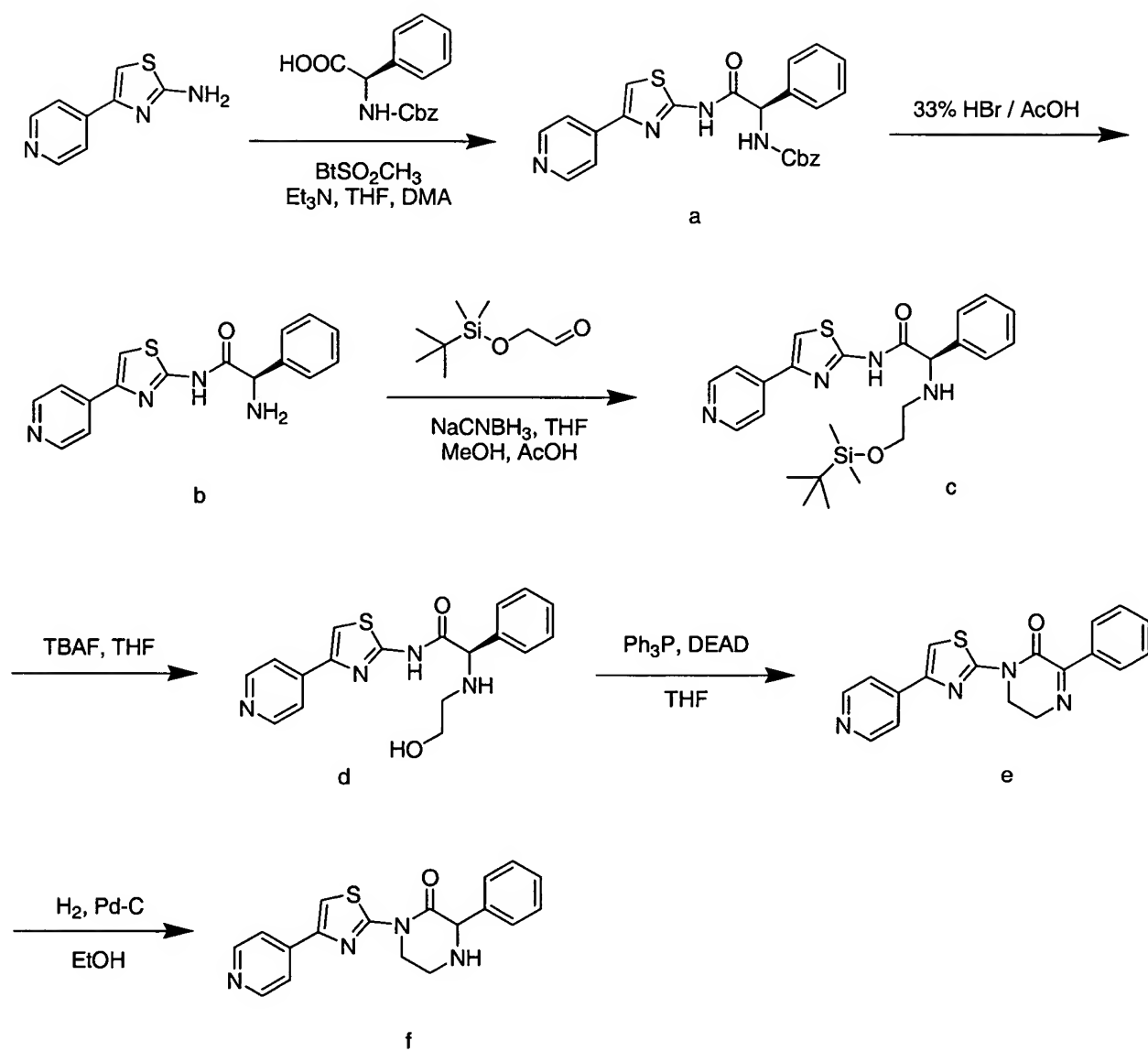


Scheme 38

[00270] 2-Phenylamino-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: A suspension of 2-chloro-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (1 mmol) and aniline (4 mmol) in n-propanol was stirred at 75 °C overnight. The reaction mixture was filtered and the filtrate was injected into preparative HPLC. ¹H NMR (500 MHz, CD₃OD) δ 4.3 (s, 2H), 6.73 (dd, 1H), 6.78 (d, 2H), 7.2 (dd, 2H), 8.3 (s, 1H), 8.47 (d, 2H), 8.79 (d, 2H). LC-MS (10-90% CH₃CN in H₂O), Rt = 3.36 min, [M+H]⁺ = 311, [M-H]⁻ = 309.

[00271] 2-(Methyl-phenyl-amino)-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: 2-Chloro-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (1mmol) and N-methylaniline (3 mmol) were suspended in dimethylacetamide and stirred at 70 °C overnight. The reaction mixture was filtered and the filtrate was injected into preparative HPLC. ¹H NMR (500 MHz, CD₃OD) δ 3.18 (s, 3H), 4.17 (s, 2H), 6.8 (d, 2H), 6.95 (dd, 1H), 7.32 (dd, 2H), 7.85 (s, 1H), 8.22 (d, 2H), 8.8 (d, 2H). LC-MS (10-90% CH₃CN in H₂O), Rt = 3.36 min, [M+H]⁺ = 329, [M-H]⁻ = 327.

[00272] Preparation of 3-Phenyl-1-(4-pyridin-4-yl-thiazol-2-yl)-piperazin-2-one



Scheme 39

[00273] [Phenyl-(4-pyridin-4-yl-thiazol-2-ylcarbamoyl)-methyl]-carbamic acid benzyl ester: To a solution of 4-pyridin-4-yl-thiazol-2-ylamine; di-hydrobromide (1.0 g, 2.95 mmol) in 60 mL THF (tetrahydrofuran), was added 1-methanesulfonyl-1*H*-benzotriazole (1.0 g, 5.08 mmol), triethylamine (1.5 mL, 10.8 mmol), and benzyloxycarbonylamino-phenyl-acetic acid (1.0 g, 3.5 mmol) at ambient temperature. The mixture was heated using an oil bath to reflux for 12 hours. After the reaction was cooled the THF was removed under vacuum, and then the reaction was diluted with 100 mL of water and extracted with ethyl acetate (2 x 125 mL). The organic extracts were combined and washed with 10% citric acid, saturated sodium hydrogen carbonate

aqueous, and brine. The organic layer was dried with sodium sulfate and concentrated *in vacuo* to give 1.7 g as a tan solid. The material was purified by crystallization from hot EtOAc-DCM (9:1: 40 mL) to give 0.7 g (54% of theory) of [phenyl-(4-pyridin-4-yl-thiazol-2-ylcarbamoyl)-methyl]-carbamic acid benzyl ester as a pale yellow solid. ¹H NMR (CD₃CN) δ 10.4 (bs,1H), 8.65 (d,2H), 7.8 (d,2H), 7.7 (s,1H), 7.6-7.3 (m,5H) 6.65 (bs,1H), 5.65 (m,1H), 5.15 (s,1H). This material was used as is in the next step.

[00274] 2-Amino-2-phenyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide; hydrobromide (b): A mixture of **a** (0.275g, 0.62mmol) in 5 mL of 33% HBr in acetic acid was prepared. The mixture was heated at 100 °C, and the mixture turned homogeneous. After stirring for 1.5 hours, the excess HBr in acetic acid was removed under vacuum to give quantitative conversion to **3** as a burnish red glass which turned to a foam under high vacuum. LC-MS (10-90% CH₃CN in H₂O), Rt = 0.31min, [M+H]⁺ = 311, [M-H]⁻ = 309.2. This material was used as is in the next step.

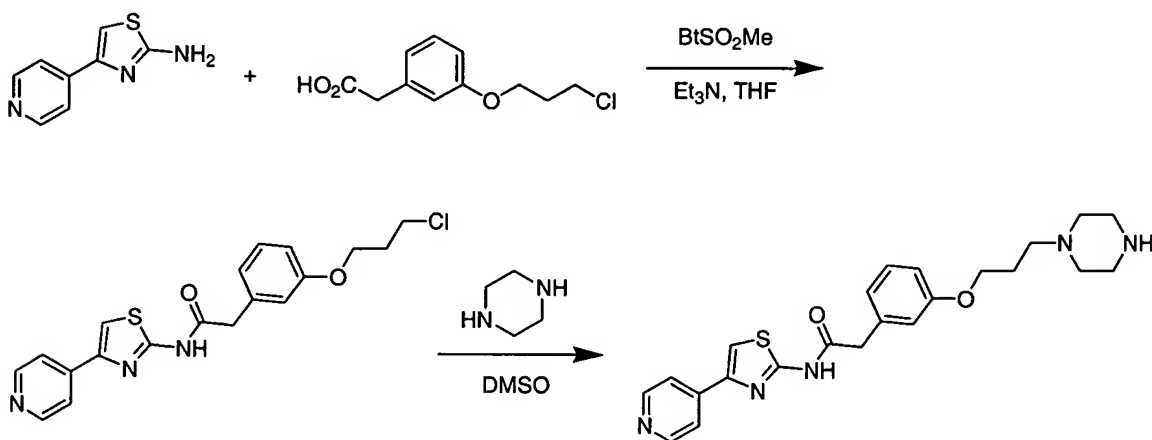
[00275] 2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethylamino]-2-phenyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (c): To a solution of **b** (0.132g, 0.28mmol) in MeOH (6mL) was added (*tert*-Butyl-dimethyl-silanyloxy)-acetaldehyde (0.059 mL, 0.308mmol), 1M sodium cyanoborohydride in THF (0.4mL, 0.4mmol), and AcOH (0.05mL). The reaction was stirred at ambient temperature for 5 hours, and then the reaction was reduced to a solid under vacuum. The solid was purified by flash chromatography on silica gel by eluting with 25-100% EtOAc-Hexanes. The product **c** obtained (40mgs, 30% of theory) as colorless glass, and used as is without further purification.

[00276] 2-(2-Hydroxy-ethylamino)-2-phenyl-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (d): To a solution of **c** (0.14g, 0.297mmol) in THF (2mL) was added 1M tetrabutylammonium fluoride solution (1.0mL, 1mmol), and the reaction was stirred for 1.0 hr. The solvent was removed and the residue was purified by flash chromatography on silica gel by eluting with 10% MeOH-EtOAc. The product **d** obtained (67mgs, 64% of theory) as brown glass. ¹H NMR (500MHz, CDCl₃, ppm) δ 8.53 (d, 2H, J=6.19Hz), 7.60 (d, 2H, J=6.18Hz), 7.36-7.20 (m, 6H), 4.06-4.02 (m, 1H), 3.76-3.73 (m, 2H), 2.90-2.71 (m, 03H), 1.55 (m, 1H), 1.30-1.67 (m, 3H), 0.87 (t, 1H, J=7.65Hz). FIA/MS [M+H]⁺ = 355, [M-H]⁻ = 353. This material was used as is in the next step.

[00277] 3-Phenyl-1-(4-pyridin-4-yl-thiazol-2-yl)-5,6-dihydro-1H-pyrazin-2-one (e): To a solution of **d** (35 mg, 0.10 mmol) in anhydrous THF was added triphenylphosphine (0.0314 g,

0.12 mmol), and diethyl azodicarboxylate (0.025 mL, 0.22 mmol). The reaction was stirred at room temperature for 1 hour or until the reaction showed no **d** remaining by HPLC. Solvent was removed from the reaction and then the material was taken up in EtOAc, and washed with brine. The residue was purified by preparative TLC chromatography on silica gel, eluting with 5% MeOH-EtOAc. The product was obtained as a colorless solid (16 mgs, 46% of theory). ¹H NMR (500MHz, CDCl₃) δ 8.60 (d, 2H, J=5.43Hz), 7.88 (m, 2H), 7.71 (m, 2H), 7.46-7.36 (m, 4H), 4.55 (t, 2H, J=6.18), 4.15 (t, 2H, J=6.18). LC-MS (10-90% CH₃CN in H₂O), Rt = 2.1min, [M+H]⁺ = 335.

[00278] 3-Phenyl-1-(4-pyridin-4-yl-thiazol-2-yl)-piperazin-2-one (f): To a solution of **e** (0.010g, 0.03mmol) in EtOH was added a catalytic amount of 10% palladium on carbon, and then the reaction was stirred under on atmosphere of hydrogen for 1.5 hour. The reaction was filtered through celite and purified by flash chromatography on silica gel by eluting with 5% MeOH-EtOAc. The product **f** obtained as a colorless glass (6.0 mgs, 60% of theory). ¹H NMR (500MHz, CDCl₃) δ 8.58 (d, 2H, J=5.97Hz), 7.71 (m, 2H), 7.46-7.18 (m, 6H), 4.78 (s, 1H), 4.50 (m, 1H), 4.20 (m, 1H), 3.40 (m, 1H), 3.25 (m, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 0.25min, [M+H]⁺ = 337(strong).

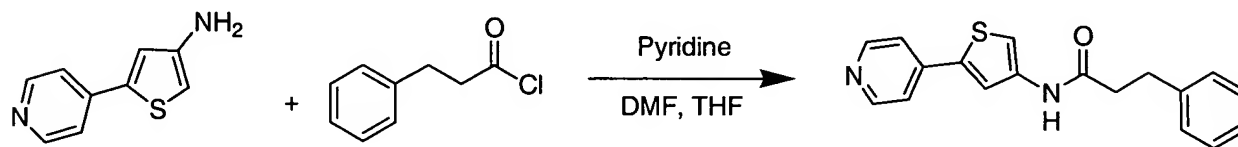


Scheme 40

[00279] 2-[3-(3-Chloropropoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: A suspension of 1-methylsulfonylbenzotriazole (2.87 g, 0.0146 mol), [3-(3-chloro-propoxy)-phenyl]-acetic acid (3.33 g, 0.0146 mol) and triethylamine (2.94 g, 0.0291 mol) was stirred at room temperature for 3 hours, then to the suspension was added 4-pyridin-4-yl-thiazol-2-

ylamine, and the reaction mixture was refluxed for 20h, then cooled to room temperature. The precipitated solid was filtered, washed and dried to afford 2-[3-(3-chloropropoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide, (2.5g, 64%). ¹H NMR (500 MHz, CD₃OD) δ 2.18 (m, 2H), 3.78 (s, 2H), 3.80 (t, 2H), 4.05 (t, 2H), 6.85 (dd, 1H), 6.9 (dd, 1H), 6.95 (d, 1H), 7.26 (dd, 1H), 7.85 (d, 2H), 8.02 (s, 1H), 8.63 (d, 2H).

2-[3-(3-Piperazin-1-yl-propoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide: A DMSO solution of 2-[3-(3-chloropropoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide (2.39 g, 6.2 mmol) and piperazine (2.12 g, 24.6 mol) was stirred at 60 °C overnight. The reaction mixture was diluted with water, then purified by preparative HPLC to afford 2-[3-(3-piperazin-1-yl-propoxy)-phenyl]-N-(4-pyridin-4-yl-thiazol-2-yl)-acetamide, 1.9g. ¹H NMR (500 MHz, DMSO-d₆) δ 2.1 (t, 2H), 3.2 (t, 2H), 3.38 (m, 8H), 3.8 (s, 2H), 4.04 (t, 2H), 6.85 (dd, 1H), 6.92 (s, 1H), 6.93 (d, 1H), 7.28 (dd, 1H), 8.17 (d, 2H), 8.33 (s, 1H), 8.8 (d, 2H), 12.65 (s, br, 1H). LC-MS (5-45% CH₃CN in H₂O, Rt = 1.34 min, [M+H]⁺ = 438, [M-H]⁻ = 436.



Scheme 41

[00280] 3-Phenyl-N-(5-pyridin-4-yl-thiophen-3-yl)-propionamide: A DMF/THF solution containing 5-pyridin-4-yl-thiophen-3-ylamine (60mg, 0.341 mmol), hydrocinnamyl chloride (76.8 mg, 0.411 mmol), and pyridine (32 mg, 0.411 mmol) was stirred at 70 °C for 3 hours, then the solvent was removed, the residue was dissolved in MeOH and purified by preparative HPLC. ¹H NMR (500 MHz, DMSO-d₆) δ 2.64 (t, 2H), 2.92(t, 2H), 7.17 (m, 1H), 7.28 (m, 4H), 7.8 (s, 1H), 7.85 (s, 1H), 7.93 (d, 2H), 8.73 (d, 2H), 10.52 (s, 1H). LC-MS (10-90% CH₃CN in H₂O), Rt = 2.30 min, [M+H]⁺ = 309, [M-H]⁻ = 307.

[00281] EXEMPLARY COMPOUNDS: It will be appreciated that a variety of compounds can be prepared according to the general methods described above. Tables 4, 5, and 6 include exemplary data for certain compounds prepared according to the general methods described above.

Table 4

COMPOUND	LC MASS PLUS	LC MASS RT
I-A-1	380	1.12
I-A-2	320	1.66
I-A-3	350	1.09
I-A-4	350	1.11
I-A-5	380	
I-A-6	354	1.24
I-A-7	338	2.3
I-A-8	398	1.56
I-A-13	370	1.63
I-A-14	370	1.3
I-A-21	372.1	2.6
I-A-29	334.13	2.08
I-A-30	309.1	1.79
I-A-31	372.9	2.17
I-A-32	325	2.04
I-A-33	296	1.61
I-A-34	356	1.62
I-A-35	326	1.64
I-A-36	330	1.7
I-A-37	374	1.66
I-A-38	346	1.76
I-A-39	356	0.94
I-A-40	326	1.11
I-A-41	347.99	2.09
I-A-42	314.09	1.73
I-A-43	310.11	1.86
I-A-44	297	1.58
I-A-45	357	1.53

I-A-46	357	1.58
I-A-47	327	1.59
I-A-48	331	1.69
I-A-49	327	1.57
I-A-50	347	1.74
I-A-51	347	1.74
I-A-53	311.1	2.23
I-A-62	348.98	2.49
I-A-63	315	1.42

Table 5

COMPOUND	LC MASS PLUS	LC MASS RT
I-B-6	356	1.67
I-B-19	296	1.65
I-B-20	326.1	1.66
I-B-21	326	1.65
I-B-22	356	0.98
I-B-23	330	1.22
I-B-24	314	1.66
I-B-25	374	1.7
I-B-33	346	1.79
I-B-34	346	1.81
I-B-44	314	1.9
I-B-49	312.25	1.49
I-B-53	346.12	2.05
I-B-54	330.16	1.87
I-B-55	310	2.1
I-B-62	302.1	2.04
I-B-65	332.1	1.65
I-B-66	332.2	1.68
I-B-67	332.1	1.82
I-B-68	332.1	1.67
I-B-69	310.2	1.73
I-B-70	380.1	2.19
I-B-71	338.2	2.18

I-B-72	409.9	2.13
I-B-73	382.1	2.05
I-B-74	324.2	2.05
I-B-75	402.2	2.24
I-B-76	346	5.9
I-B-77	346	5.29
I-B-78	322.1	2.02
I-B-79	326	4.62
I-B-80	427.2	2.1
I-B-81	340.06	1.7
I-B-82	402.1	2.47
I-B-83	312	3.53
I-B-85	311	3.49
I-B-86	326	4.45
I-B-87	351.1	3.29
I-B-88	367.2	
I-B-89	390.10348	1.72
I-B-90	328.1	1.9
I-B-91	381.9	2.23
I-B-92	348	1.3
I-B-93	348	1.94
I-B-94	350.1	1.8
I-B-95	348	1.66
I-B-96	396	2.41
I-B-97	346.1	1.92
I-B-98	336.1	
I-B-99	336.1	1.84
I-B-100	352.1	1.46
I-B-101	308.1	2.02
I-B-102	332.1	1.77
I-B-103	324.1	2.3
I-B-104	328	1.75
I-B-105	328.1	2.11
I-B-106	337.1	1.5
I-B-107	342.1	1.36
I-B-108	311	3.13
I-B-109	324.1	1.99
I-B-110	324.1	1.97
I-B-111	325	3.9
I-B-112	325	3.92

I-B-113	343.1	1.38
I-B-114	361.1	1.56
I-B-115	326.1	1.66
I-B-116	340.1	1.75
I-B-117	342.1	1.39
I-B-118	310.1	1.82
I-B-119	344	2.17
I-B-120	359	1.83
I-B-121	328.1	1.92
I-B-122	355.1	1.58
I-B-123	337.1	1.58
I-B-124	339.2	3.84
I-B-125	339.1	4.32
I-B-126	348	3.88
I-B-127	328	2.89
I-B-128	342	3.54
I-B-129	345.9	4.33
I-B-130	330	3.68
I-B-131	312	1.67
I-B-132	342	1.71
I-B-133	354.1	1.67
I-B-134	348	1.92
I-B-135	354.1	1.64
I-B-136	330	1.75
I-B-137	346	
I-B-138	356.1	1.71
I-B-139	363.1	4.88
I-B-140	363.1	4.84
I-B-141	326	1.96
I-B-142	364	2.05
I-B-143	355.1	1.25
I-B-144	348	1.8
I-B-145	363	4.92
I-B-146	343	2.13
I-B-147	351.1	2.77
I-B-148	421.9	1.96
I-B-149	421.9	1.95
I-B-150	343	
I-B-151	357	4.88
I-B-152	340	2.01
I-B-153	328.1	2.31

I-B-154	360.1	2.71
I-B-155	328	5.09
I-B-156	360	3.77
I-B-157	343.9	3.36
I-B-158	359	2.64
I-B-159	377	2.89
I-B-160	392.9	3.8
I-B-161	373	3.3
I-B-162	348	3.93
I-B-163	342.1	3.81
I-B-164	302	1.62
I-B-165	340	2.1
I-B-166	335	1.9
I-B-167	311	1.88
I-B-168	341	2.25
I-B-169	329.1	2.21
I-B-170	329.2	1.84
I-B-171	343	1.1
I-B-174	363	2.1
I-B-175	375.2	1.78
I-B-176	435.9	
I-B-177	325	2.1
I-B-178	355.1	2.21
I-B-179	417.8	2.2
I-B-180	373.9	2.1
I-B-181	477.9	
I-B-183	351	2.2
I-B-185	389.9	1.8
I-B-186	433.8	1.8
I-B-187	431.9	2.4
I-B-190	402	2.7
I-B-191	329.9	2.5
I-B-192	423.1	0.4
I-B-193	439.1	0.86
I-B-194	443	1.5
I-B-197	347.9	2.8
I-B-198	360	2.9
I-B-199	437.1	2.4
I-B-200	453.1	2.15
I-B-201	457	2.4
I-B-202	423.2	1.8

I-B-203	453.2	2.24
I-B-204	356	1.4
I-B-205	423.1	2.17
I-B-206	397	2.03
I-B-207	437.1	2.3
I-B-208	438.6	1.34
I-B-209	452.1	1.75
I-B-210	412.9	1.96
I-B-211	383.1	1.92
I-B-212	427.1	0.75
I-B-213	453.4	2.14
I-B-214	467.2	2.03
I-B-215	439.2	1.97
I-B-216		1.99
I-B-217	383.1	1.63
I-B-218	423.1	2.1
I-B-219	424.1	1.09
I-B-220	438.2	1.55
I-B-221	399.1	1.56
I-B-222	369.1	1.62
I-B-223	413.1	1.5
I-B-224	427	2.13
I-B-225	439.1	1.24
I-B-226	451.3	1.13
I-B-227	425.1	1.12
I-B-228	381.1	
I-B-229	445	2.2
I-B-230	414	2.6
I-B-231	436.1	1.4
I-B-232	397	1.61
I-B-233	397	1.59
I-B-234	417	1.75
I-B-235	427	1.12
I-B-236	427	1.23
I-B-237	385	1.22
I-B-238	367	1.21
I-B-239	447	1.28
I-B-241	313.1	1.8
I-B-242	331.1	2.06
I-B-243	327.1	2.17

I-B-244	323.1	2.23
I-B-245	359.1	2.57
I-B-246	373	2.13
I-B-247	329	2.11
I-B-248	347	2.18
I-B-249	363	2.42
I-B-250	416.9	2.19
I-B-251	372.9	2.16
I-B-252	325.1	2.01
I-B-253	313.1	2.05
I-B-257	343	6.74
I-B-258	357.1	3.84
I-B-261	330	4.84
I-B-262	344	5.44
I-B-263	387.1	4.98
I-B-264	400.7	5.42
I-B-265	370.1	5.69
I-B-266	384.1	6.96
I-B-267	315.1	2.91
I-B-268	315.1	2.96
I-B-269	344.9	3.3
I-B-270	311	3.13
I-B-271	327	2.84
I-B-272	330.9	3.25
I-B-273	297	2.88
I-B-274	327	2.88
I-B-275	340	2.2
I-B-276	354.1	2.3
I-B-277	389.9	1.9
I-B-278	314	
I-B-280	340.0	2.20
I-B-281	354.1	2.3
I-B-282	389.9	1.9
I-B-283	354.1	2.3
I-B-286	380.1	2.5
I-B-287	354.1	2.4
I-B-288	354.1	2.5
I-B-289	366.10	2.40
I-B-290	437.2	2.39

I-B-292	466.2	1.65
I-B-293	420.2	2.11
I-B-299	346.1	3.17
I-B-306	452.2	1.8
I-B-307	466.2	1.9
I-B-308	451.2	2.68
I-B-309	466.2	1.4
I-B-310	296.0	3.3
I-B-311	310.0	3.5
I-B-312	465.2	2.48
I-B-315	479.2	3.76
I-B-316	314.0	2.9
I-B-317	314.0	2.8
I-B-318	332.0	2.9
I-B-319	328.0	3.1
I-B-320	320.0	1.58
I-B-321	326.2	1.89
I-B-323	430.2	2.29
I-B-324	338.2	2.16
I-B-325	380.2	2.54
I-B-326	389.2	1.72
I-B-327	403.2	1.92
I-B-328	354.3	2.47
I-B-329	338.2	2.65
I-B-330	356.3	2.79
I-B-331	420.1	2.8
I-B-332	404.2	2.0
I-B-333	326.0	1.9
I-B-334	340.0	2.0
I-B-335	403.1	1.89
I-B-336	389.1	1.72
I-B-339	352.2	1.9
I-B-340	335.0	0.25
I-B-341	335.1	2.1
I-B-342	336.98	0.25
I-B-343	336	2.3
I-B-344	372.1	2.4
I-B-345	374.0	1.0
I-B-346	314.00	2.0
I-B-347	437.3	2.13

Table 6

COMPOUND	LC MASS PLUS	LC MASS RT
I-C-1	309	2.3
I-C-2	325	2.05
I-C-3	329	2.67
I-C-4	295	1.92
I-C-5	325	2.17
I-C-6	313	2.21
I-C-7	372.9	2.5
I-C-8	351.2	1.17
I-C-9	437.2	0.88
I-C-10	438.1	1.79
I-C-11	335	2.1
I-C-12	363	2.5
I-C-13	356	1.51
I-C-14	356	1.63
I-C-15	326	1.65
I-C-6	330	1.74
I-C-17	326	1.63
I-C-18	374	1.71
I-C-19	296	1.42
I-C-20	346	1.61
I-C-21	348	2.47
I-C-22	314.04	1.99
I-C-23	310.1	
I-C-24	331.0	1.99
I-C-26	420.9	1.86
I-C-27	329.0	2.10
I-C-28	389.1	1.87
I-C-29	326.1	2.84
I-C-30	408.95	2.42
I-C-31	313.0	1.92
I-C-32	239.0	2.3
I-C-33	332.0	3.0
I-C-34	345.1	2.34
I-C-35	314.0	4.63
I-C-36	389.1	1.77
I-C-37	311.0	1.50
I-C-38	325	1.9
I-C-39	435.0	2.10

I-C-40	370.20	
I-C-41	371.0	2.7
I-C-42	374.2	3.23
I-C-43	310.0	3.16
I-C-44	438.4	1.39
I-C-45	452.4	2.42
I-C-46	437.1	3.34
I-C-47	465.2	3.35

[00282] BIOLOGICAL TESTING

[00283] Example 1: ROCK INHIBITION ASSAY

[00284] Compounds were screened for their ability to inhibit ROCK I (AA 6-553) activity using a standard coupled enzyme system (Fox et al. (1998) *Protein Sci.* 7, 2249). Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 2 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 45 μ M ATP (Sigma Chemicals, St Louis, MO) and 200 μ M peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 45 nM ROCK I. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 350 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

[00285] Compounds of the invention were found to inhibit ROCK. In certain embodiments, compounds were shown to have a K_i of less than 1 μ M for ROCK

[00286] Example 2: ERK INHIBITION ASSAY

[00287] Compounds were assayed for the inhibition of ERK2 by a spectrophotometric coupled-enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay, a fixed concentration of activated ERK2 (10 nM) was incubated with various concentrations of the compound in DMSO (2.5 %) for 10 min. at 30°C in 0.1 M HEPES buffer, pH 7.5, containing 10 mM MgCl₂, 2.5 mM phosphoenolpyruvate, 200 μ M NADH, 150 μ g/mL pyruvate kinase, 50 μ g/mL lactate dehydrogenase, and 200 μ M erktide peptide. The reaction was initiated by the addition of 65 μ M ATP. The rate of decrease of absorbance at 340 nM was monitored. The K_i was determined from the rate data as a function of inhibitor concentration.

[00288] Compounds of the invention were found to inhibit ERK2. In certain embodiments, compounds were shown to have a K_i of less than 1 μ M for ERK2

[00289] Example 3: GSK INHIBITION ASSAY

[00290] Compounds were screened for their ability to inhibit GSK-3 β (AA 1-420) activity using a standard coupled enzyme system (Fox et al. (1998) *Protein Sci.* 7, 2249). Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 300 μ M NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 20 μ M ATP (Sigma Chemicals, St Louis, MO) and 300 μ M peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 20 nM GSK-3 β . Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

[00291] An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μ l) was incubated in a 96 well plate with 5 μ l of the test compound of interest at final concentrations spanning 0.002 μ M to 30 μ M at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in daughter plates. The reaction was initiated by the addition of 20 μ l of ATP (final concentration 20 μ M). Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30°C. The K_i values were determined from the rate data as a function of inhibitor concentration.

[00292] Compounds of the invention were found to inhibit GSK3. In certain embodiments, compounds were shown to have a K_i of less than 1 μ M for GSK3.

[00293] Example 4: PKA Inhibition Assay

[00294] Compounds were screened for their ability to inhibit PKA using a standard coupled enzyme assay (Fox et al., *Protein Sci*, 1998, 7, 2249). Assays were carried out in a mixture of 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl , 1 mM DTT and 3% DMSO. Final substrate concentrations in the assay were 50 μ M ATP (Sigma Chemicals) and 80 μ M peptide (Kemptide, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 18 nM PKA. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

[00295] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP, and the test compound of the present invention. 55 μ l of the

stock solution was placed in a 96 well plate followed by addition of 2 μ l of DMSO stock containing serial dilutions of the test compound of the present invention (typically starting from a final concentration of 5 μ M). The plate was preincubated for 10 minutes at 30°C and the reaction initiated by addition of 5 μ l of ATP (final concentration 50 μ M). Initial reaction rates were determined with a Molecular Devices SpectraMax Plus plate reader over a 15 minute time course. IC₅₀ and K_i data were calculated from non-linear regression analysis using the Prism software package (GraphPad Prism version 3.0a for Macintosh, GraphPad Software, San Diego California, USA).

[00296] Compounds of the invention were found to inhibit PKA. In certain embodiments, compounds were shown to have a K_i of less than 1 μ M for PKA.